



# **Acta Medica Scandinavica**

*Published by The Almqvist & Wiksell Periodical Company Stockholm, Sweden*

**Vol. 206 No. 1-2 1979**



# Acta Medica Scandinavica

## TABLE OF CONTENTS

VOLUME 206, 1979

*Ed to al* Inactivation of one of the X chromosomes in females is a biological phenomenon of clinical importance

*M N Hamers D W se A Ejofor A Stryland D Rob nson and J M Tager* Relationship between biochemical and clinical features in an English Anderson Fabry family

*G Kollner and J G Lj nggren* T<sub>3</sub> and reverse T<sub>3</sub> determinations in connection with the TRH test in the evaluation of possible hyperthyroidism

*M Blclert Toft J Egedorf C Christensen and C K Axelsson* Function of pituitary thyroid axis after surgical treatment of non toxic nodular goitre

*O R Nilsson B E Ka lberg B Kagedal L Tegler and S Almq st* Non selective and selective  $\beta$  1 adrenoceptor blocking agents in the treatment of hyperthyroidism

*F K Reme* Angiotensin-converting enzyme in sarcoidosis

*I Tuesson E Benito p and O Zettervall* The expression of a human B lymphocyte antigen on cells in different types of leukaemia

*I Tuesson E Berntorp and O Zettervall* The expression of a human B-lymphocyte antigen and surface membrane immunoglobulin by lymphoid cells from patients with lymphocytic lymphoma multiple myeloma and benign monoclonal gammopathy

*B Lant B Calmark and P Renstén* Electrolytes and whole body potassium in acute leukemia

*A Heath and D Selander* Self poisoning treated in the ICU

*L R Erla dt M Sedegholm and I Gert* Emergency room resuscitation of patients with cardiac arrest out of hospital Outcome and immediate prognosis in 319 patients

*M H Frick P T Harjola and M Valle* Work status after coronary bypass surgery A prospective randomised study with ergometric and angiographic correlations

*R Nordlander and O Nyquist* Mortality arrhythmias and pump failure in acute myocardial infarction in relation to estimated infarct size

*P Andersson and L Lundkv st* The QT syndrome—A family description

*A Ponka* Carditis associated with mycoplasma pneumoniae infection

*G Ahlman G Ahlberg H Saetre I Haglund and M Korsgren* A controlled study of early discharge after uncomplicated myocardial infarction

*L Jönasson G Nordlander U Hedner and I M Nilsson* Comparison of streptokinase with heparin Late results in the treatment of deep venous thrombosis

*U Wae n and H Åberg* Blood pressure in 60-year-old men Findings in a health survey at some comparisons with 50-year-old men in the same community

*T P Kajar P Ylalo T Metsä Ketela and H Vapaa alo* The effects of a beta blocking agent atenolol on blood pressure plasma renin activity and prostaglandin F<sub>2a</sub> excretion on patients with essential hypertension



# Table of contents

<i>Bernung H Egeblad P Laundsen and A Wennervold</i> The diagnostic challenge of left atrial myxoma. Importance of echocardiographic screening	115
<i>G Tornvall and C O N</i> Massive embolization of cardiac myxoma. A case report	123
<i>E Örtengren</i> Diastolic wave initiating ventricular tachyarrhythmias and suppressible by lignocaine and isoprenaline	127
<i>W A Veenhoven H J Oosterhuis and G S van der Schans</i> Myasthenia gravis and Werlhof's disease	131
<i>T Dickler and P O Wester</i> Effects on muscle electrolytes of potassium and magnesium infusions, spironolactone medication and operation in a case of primary aldosteronism	137
<i>E Hagg F Lithner B Lindqvist and F Ekström</i> The syndrome of inappropriate secretion of an antidiuretic hormone. A case report	141
<i>S Ljungberg S Å Forsberg S Paulin and L Werko</i> Coronary arteriography in 486 patients—Arteriographic pathology and prognosis	145
<i>J Brenne O J Ohm and L Segadal</i> Sick sinus syndrome treated with permanent pace maker in 109 patients. A follow-up study	153
<i>O Störtebecker and L Ejsland</i> Aortic valve replacement in elderly patients	161
<i>G Burek L R Erhardt and G Lindberg</i> Prediction of survival in patients with acute myocardial infarction. A clinical study on 100 consecutive patients	165
<i>J Lindvall L R Erhardt T Lundman A Rehnqvist and A Sjögren</i> Early mobilization and discharge of patients with acute myocardial infarction. A prospective study using risk indicators and early exercise tests	169
<i>J Hultberg</i> Arrhythmias in the coronary care unit recognized with the aid of automated ECG monitoring. A twelve-month study in 679 patients	177
<i>G Forssell P Nordander O Åquist and A Schenck-Gustafsson</i> Intraaortic balloon pumping in the treatment of cardiogenic shock complicating acute myocardial infarction	189
<i>J Fischer Hansen and O Pedersen-Bjergaard</i> Q waves and coronary artery disease	193
<i>L Stenow</i> Familial occurrence of intracranial aneurysms	197
<i>A G Hult B E Nilsson A E Westlin and P E Willund</i> Alkaline phosphatase in women with osteoporosis	201
<i>A G Hult B E Nilsson A E Westlin and P E Willund</i> Bone biopsy in women with spinal osteoporosis	205
<i>V Rafnsson C Bengtsson J Lennartsson O Lindqvist H Norrby and F Tibblin</i> Erythrocyte sedimentation rate in a population sample of women with special reference to its clinical prognostic significance	207
<i>n J F Pehfeld and F Stadl</i> Small cell carcinoma of the lung: Relation of calcitonin, marrow metastases, parathormone and gastrin	215
<i>on and P Lundin</i> Multiple attacks of jaundice associated with repeated sulfonamide	219
<i>J Öberg H Bostrom J Fahrenkrug J F Dymberg O B Schaffalitzky de Muckadell and G Lindqvist</i> Streptozotocin treatment of a pancreatic tumour producing VIP and gastrin associated with Verner Morrison syndrome	223
<i>P V Luoma M I Reunanen and E A Sotaranta</i> Changes in serum triglyceride and cholesterol levels during long term phenytoin treatment for epilepsy	229
<i>D J van Rhenen M I Koolen Th M Feltkamp-Vroom and R S Weening</i> Immune complex glomerulonephritis in chronic granulomatous disease. Case report of an eighteen year-old girl	233
<i>A Arnung and I Lind A E Jensen</i> Temporal arteritis and gangrene of the tongue	239
<i>P Arneborn and J Palmblad</i> Drug induced neutropenias in the Stockholm region 1976-1977	241
<i>C Sonnhag E Karlsson and J Hult</i> Procainamide induced lupus erythematosus-like syndrome in relation to acetylator phenotype and plasma levels of procainamide	245
<i>T Jonason B Jonson I Rönqvist and A Öman-Rydberg</i> Effect of physical training on different categories of patients with intermittent claudication	253
<i>O Selroos and E Korhonen</i> Prognostic significance of lymphopenia in sarcoidosis	259
<i>G Blohme and J Waldenström</i> Glibenclamide and glipizide maturity onset diabetes. A double blind cross-over study	263
<i>O B Schaffalitzky de Muckadell H Mortensen and J Lyngsøe</i> Metabolic effects of glucocorticoid and ethanol administration in phenformin- and metformin treated obese diabetics	269

- H Stabler S Borg and C Allgulander* Clinical significance of abnormal heterogeneity of transferrin in relation to alcohol consumption
- J Sellæg and K Søllæg* Free light chains of immunoglobulins in amyloidosis
- E Önnäs* Prognosis in hypertrophic obstructive cardiomyopathy
- S-O Isacson and B W Johansson* Myocardial infarction in Malmö during the 10-year period 1963-1972
- A Rehnqvist and T Lundman* Dobutamine in left heart failure after acute myocardial infarction
- O R Nilsson B E Karlberg O Ohlsson T Thulin and A Tolagen* Atenolol administered once daily in primary hypertension. Effects on blood pressure in relation to pre treatment plasma renin activity
- J Wahren H Linderholm and P Felg* Amino acid metabolism in patients with a hereditary myopathy and paroxysmal myoglobinuria
- L Elsborg and J Mosbech* Pernicious anaemia as a risk factor in gastric cancer
- H Olsson and L Brandt* Relief of pruritus as an early sign of spinal cord compression in Hodgkin's disease
- B Lonnqvist G Gahrton P Eriksson A Friberg and L Zech* Isochromosome 17 in a patient with a myeloproliferative disorder terminating in eosinophilic leukemia
- M Dan elson and J Nordenstrom* Isoosmotic hemodilution in erythrocytosis secondary to chronic obstructive lung disease
- P Harmsen G Berglund O Larsson G Tibblin and L W Thelmsen* Stroke registration in Göteborg Sweden 1970-75. Incidence and fatality rates
- S Einhorn H Blomgren K Cantell and H Strander* Effect of prolonged *in vivo* administration of leukocyte interferon on the mitogen responsiveness of human lymphocytes
- L A Carlson L E Böttger and P E Åkfeldt* Risk factors for myocardial infarction in the Stockholm prospective study. A 14-year follow-up focussing on the role of plasma triglycerides and cholesterol
- G Bragegard R Hallgren P Venge and L W de* Serum ferritin during inflammation. A study on myocardial infarction
- R Lofmark* Clinical features in patients with recurrent myocardial infarction
- E Loogna L Kaizer and L A Carlson* Effect of plasma free fatty acid lowering on exercise tolerance and ST segment depression in patients with angina pectoris
- K Forfang H Rostad S Sorland and A Levorstad* Late sudden death after surgical correction of coarctation of the aorta. Importance of aneurysm of the ascending aorta
- L Tibblin and B Wranne* Oesophageal symptoms and manometry in valvular heart disease
- A Landmark L Storstein and A Larsen* Disopyramide plasma levels in cardiac patients on maintenance therapy
- H Hey A Vest Aelsen B Lund Bj Lund and O H Sørensen* Reduced vibratory perception and corneal sensitivity and metabolic disturbances following intestinal bypass surgery
- M Juuti and O P Heinonen* Incidence of urolithiasis leading to hospitalization in Finland
- C-G Lofdahl L Solvell A B Laurell and B R Johansson* Systemic capillary leak syndrome with monoclonal IgG and complement alterations. A case report on an episodic syndrome
- B R Johansson and C-G Lofdahl* Ultrastructure of the microvessels in skeletal muscle in a case of systemic capillary leak syndrome
- B Stenius Aarnala and P Tukia nen* Miliary tuberculosis
- L E Wille P Wetteland O Forre T Hovig and M Winnem* An atypical manifestation of multiple myeloma in a 24-year-old male
- G Hillerdal B Marjanovic and H Åberg* Rheumatoid arthritis. Immune complex disease and hypereosinophilic syndrome. Report on a case
- L Werko* Diet lipids and heart attacks
- P E Lins S Efendic and A Hall* Effect of 24-hour somatostatin infusion on glucose homeostasis and on the levels of somatomedin A and pancreatic and thyroid hormones in man
- L Juhlin and W B Sheller* Diagnostic sign of hypoglycemia. Persistent movement of neutrophil granules
- L Moln and O Stendahl* The effect of sulfasalazine and its active components on hemophagocytic leukocyte function in relation to ulcerative colitis

Kallner and J G LjunÅgren The role of endogenous cortisol in patients with non thyroidal illness and decreased T <sub>3</sub> levels	459
Watt, I Ek and S BjÅkdeman Noninvasive diagnosis of acute deep vein thrombosis. A comparison between thermography plethysmography and phlebography	463
Ekestrom B Eklund L Liljeqvist and O Nordhus Non invasive methods in the evaluation of obliterative disease of the subclavian or innominate artery	467
L Liem J H ten Veen A I Lie T E W Felikamp and D Durrer Incidence and significance of heartmuscle antibodies in patients with acute myocardial infarction and unstable angina	473
McCull D Linfeldt A Vedin C Wilhelmsson H Wedel and L Wilhelmsen Influence of a myocardial infarction on blood pressure and serum cholesterol	477
Å Forsberg and S Juul Møller Myocardial infarction complicated by heart block—Treatment and long term prognosis	483
Å Falch A Quist Paulsen A E Ødegaard and N Norman Central and renal circulation renin and aldosterone in plasma during prazosin treatment in essential hypertension	489
Gudbrandsson L Hansson H Herlitz and L Andren Malignant hypertension—Improving prognosis in a rare disease	495
Noppa C Bengtsson B Isaksson and U Smith Adipose tissue cellularity—Metabolic aspects. The population study of women in Göteborg 1974–1975	501
Wibell P A Dahlberg and A Karlsson Hyperparathyroidism associated with distal tubular dysfunction but intact reabsorption of protein in the proximal tubules	507
Østergaard Kristensen Labetalol induced Peyronie's disease? A case report	511

## EDITORIAL

# Inactivation of One of the X Chromosomes in Females Is a Biological Phenomenon of Clinical Importance

sex chromosome constitution is fundamentally different between male and female members of mammalian species. Females have a pair of equal chromosomes (X chromosomes) whereas males have one X chromosome and one much smaller chromosome the Y chromosome in the sex chromosome pair. The sex of the zygote is dependent upon which sex chromosome is present in the second chromosome set of the sperm cell fertilizing the egg and the difference in sex chromosome constitution between male and female conceptuses is the basis for their divergent sexual differentiation and development.

A great number of genes not related to sexual development are known to reside in the X chromosome. One might have expected that the effect of these genes would be much more pronounced in males who have two X chromosomes than in females who have only one. This expectation however does not materialize. Healthy males and females have about the same level of the enzyme glucose-6-phosphate dehydrogenase (G6PD) as well as of blood clotting factor VIII. Both proteins are determined by genes on the X chromosome. Work by *Drosophila* geneticists antedates that of mammalian geneticists in this area by a good many years. The fact that X-linked genes (genes on the X chromosome) in *Drosophila* have a similar expression in males and females was established at an early stage and H. J. Muller introduced dosage compensation for the regulatory mechanism which appeared to be operating.

Less than 20 years ago Mary Lyon and other workers addressed themselves to the question of age compensation in mammals. Lyon (7) studied colour patterns in mice who were heterozygous for X-linked genes determining these traits. She put forward the hypothesis that the mottling phenotypes caused by X-linked genes were the result of regulation of X chromosome function. She postulated that in a given somatic cell of a female mammal only one of the two X chromosomes is

active and that this is the result of inactivation of one X chromosome early in the development of the zygote. She suggested that it is random whether the maternal or the paternal X chromosome becomes inactivated but that once the inactivation process has taken place the same X chromosome will be inactivated in all daughter cells of the original cell.

In the years since Mary Lyon published the first paper on her hypothesis in 1961 confirmatory evidence has come from many studies. Today this biological phenomenon may well be referred to as the *Lyon principle* rather than the *Lyon hypothesis*. Early and important evidence for the validity of this concept in man originated from studies on females who were heterozygous for G6PD deficiency. In such heterozygotes two populations of red blood cells were demonstrated, one possessing and one lacking G6PD activity as predicted by Mary Lyon's hypothesis. Also cell clones established from skin biopsies of females heterozygous for electrophoretic variants of G6PD turned out to have characteristics different from mass culture cells. Both G6PD alleles were expressed in the latter whereas the product of only one allele could be demonstrated in the clones. This showed that only one of the X-linked alleles was active in the cell from which the clone originated and also that the pattern of X chromosome inactivation had persisted through cell divisions. This was a direct confirmation of Lyon's prediction that once the inactivation phenomenon had taken place it would always be the same X chromosome which was inactivated in all the progeny of that cell.

In the years since these important experiments were conducted similar studies have been made on the behaviour of other X-linked enzymes. Thus two cell populations have been found in heterozygotes for hypoxanthine guanine phosphoribosyl transferase (HGPRT) deficiency, phosphoglycerate kinase variants,  $\alpha$ -galactosidase deficiency and phosphorylase B kinase deficiency. Also heterozygotes for Hunter's disease exhibit two cell

populations with respect to cellular mucopolysaccharide accumulation

The cytological expression of the inactivated X chromosome is the sex chromatin body or the Barr body which is present in the nucleus of cells from females. Only one X chromosome is active even in individuals with more than two X chromosomes. In these individuals the number of Barr bodies will be the number of X chromosomes minus one.

Whereas the paternal and maternal X chromosomes have an equal chance of becoming inactivated in cells with a normal karyotype, cells with structural X chromosome anomalies behave distinctly different. Thus human cells with X chromosome deletions exhibit inactivation of the abnormal X chromosome. In non reciprocal translocations in humans the rearranged X chromosome is the one which becomes inactivated.

Both X chromosomes are active in oocytes. It appears that two active X chromosomes are necessary for normal meiosis. Females with Turner's syndrome who have only one X chromosome (karyotype XO) are sterile. Two functional X chromosomes seem to be necessary for normal development of the ovaries. There is evidence that for normal spermatogenesis in males the X chromosome needs to become heterochromatic.

It was originally thought that the whole X chromosome is subject to inactivation. Elegant studies of women who were heterozygous at more than one X linked locus have supported this view.

The linkage phase is known in such women and predictions can be made concerning the expression of both enzymes in individual cells or cell populations if the genes for two enzyme deficiencies are coupling (on the same member of the X chromosome pair). A given cell would exhibit neither or both enzyme activities. Such studies have shown that two enzyme loci on the same X chromosome are either both active or both inactive as predicted by the original hypothesis. Nevertheless it is not clear that every X linked locus is inactive. Thus there is some evidence that the locus for the Xg blood group system is not inactivated. Heterozygotes appear to have one red cell population only. However, this would not necessarily mean that both Xg loci are active in heterozygotes. Very little is known about the biochemistry of the Xg(a) antigen. Hypothetically it could even become adsorbed to the red cells following synthesis by other cells.

The exact timing of the inactivation event is not known. However studies in the mouse have revealed differences in fluorescence between the X chromosomes in embryos with more than 40 cells (early blastula stage) but not earlier. This problem has also been approached by studies of enzyme activity controlled by X linked genes in early mouse embryos. The expectation would be that inactivation of one X chromosome has taken place whenever a unimodal distribution of enzyme activity is observed since the difference between male and female embryos before X chromosome inactivation should result in a bimodal distribution. Such enzyme analyses conducted on mouse embryos were in agreement with the results from cytological studies. There is now good evidence that the inactivation in the mouse occurs between the morula and early blastocyst stages. This evidence correlates from studies on the activity of the X linked enzyme HGPRT (2, 5).

From a functional point of view the inactivation of one of the X chromosomes in somatic cells of females effectively causes a mosaic condition. Heterozygotes for deficiencies of X linked enzyme will be present in one cell population but not in the other. Since it is random which one of the two X chromosomes becomes inactivated the fraction of cells in which the chromosome with the gene specifying the normal enzyme is active may occasionally be very high or very low. This has consequences of clinical importance. Thus females who are heterozygous for hemophilia A exhibit a wide spectrum of coagulation factor VIII concentrations and the levels will be within normal limits if by chance there are many cells which have the X chromosome carrying the gene for normal factor VIII as the active one. Thus there are good biological reasons for the difficulty in detecting a significant fraction of carriers of X linked disorders. This is true not only for the detection of carriers of hemophilia but also for attempts to detect the carrier state for the Duchenne type muscular dystrophy by means of creatine kinase activity determination.

The opposite extreme of normal coagulation factor VIII levels is the occasional manifestation of clinical hemophilia in heterozygous females. Thomsen and Holmberg et al (4) reported on a woman who clinically manifest hemophilia B but was a heterozygote. This was definitely proven by the fact that she had given birth to a healthy boy with

normal masculine karyotype. Since his only X chromosome came from the mother, she must have had the gene for normal coagulation factor VIII on one of her X chromosomes. Before the event of the Lyon principle, a reasonable interpretation of the occurrence of a chromosomally normal female with haemophilia would be that of heterozygosity in combination with a new mutation (provided that the father of the woman was healthy).

In this issue, Hamers et al. (3) report studies on a kindred with Fabry's disease. In this X-linked disorder,  $\alpha$ -galactosidase activity is significantly reduced and the clinical picture is dominated by pain and skin lesions and renal failure at later stages. The patients lack the A isoenzyme of  $\alpha$ -galactosidase and there is an accumulation of ceramide trihexoside in blood vessels, the nervous system, kidneys, cornea and other tissues.

The manifestations of Fabry's disease in heterozygous females represent an excellent clinical illustration of the fundamental biological phenomenon of Lyonization. Depending on the number of cells which have the X chromosome with the normal gene inactivated, the clinical manifestations vary greatly. Thus, not all heterozygotes among the patients of Hamers et al. had pain or skin lesions, whereas others were severely affected. Interestingly, the clinical manifestations did not necessarily reflect the enzyme level as detected by the methods used. Clearly, the manifestations in heterozygous females are modified by other factors, hereditary or environmental. A given gene operates within the total genotype of the individual and the genetically determined biochemical reactions may be influenced by environmental and nutritional factors. As so often in clinical medicine, we are faced with a situation where we must consider heredity and environment, not only one to the exclusion of the other.

An important finding in the kindred studied by Hamers et al. was that of dissimilar  $\alpha$ -galactosidase expression in monozygotic twins. This argues strongly against the possibility that X chromosome inactivation should be non-random in heterozygotes for this disease, as had been suggested.

In X-linked nephrogenic diabetes insipidus, a partial defect is also demonstrable in females. The varying manifestations in such females suggest that in this disorder, as well as the phenomenon of X chromosome inactivation, may be a cause for clinical variation. Several other cases of varying clinical

manifestations in females, probably caused by Lyonization, could be listed. However, the above examples may suffice to illustrate the need to be aware of X chromosome inactivation for the understanding of variability in clinical manifestations and of the problems inherent in attempts to detect female carriers of X-linked disorders.

The insight into regulation of X chromosome function which has followed in the years since the Lyon principle was first formulated, has made possible several new approaches in medical research. Linder and Gartler (6) could demonstrate that uterine myomas originate from one single cell by examining X-linked enzymes in such material from heterozygous females. A similar approach, whereby cellular monotypy was found, formed the basis for Benditt's hypothesis (1) that atherosclerotic lesions originate from one single parent cell. Data which appear to confirm this finding have been published, pointing to a genetic event in a somatic cell as an important cause for such lesions. Thus, clinical as well as experimental medicine has benefited significantly from the work on X chromosome inactivation in mammals, which was started a mere 20 years ago.

Kare Berg

Institute of Medical Genetics  
University of Oslo, Norway

## REFERENCES

1. Benditt E. P. & Benditt J. M. Evidence for a monoclonal origin of human atherosclerotic plaques. *Proc. Natl. Acad. Sci. USA* 70: 1753, 1973.
2. Epstein C. J., Smith S., Travis B. & Tucker G. Both X chromosomes function before visible X chromosome inactivation in female mouse embryos. *Nature* 274: 500, 1978.
3. Hamers M. N., Wise D., Eijfor A., Strjland A., Robinson D. & Tager J. M. Relationship between biochemical and clinical features in an English Anderson-Fabry family. *Acta Med. Scand.* 206: 5, 1979.
4. Holmberg L., Nilsson I. M., Henniksson P. & Ørstavik K. H. Homozygous expression of haemophilia B in a heterozygote. *Acta Med. Scand.* 204: 321, 1978.
5. Kratzer P. G. & Gartler S. M. HGPRT activity changes in preimplantation mouse embryos. *Nature* 274: 503, 1978.
6. Linder D. & Gartler S. M. Glucose-6-phosphate dehydrogenase mosaicism: utilization as a cell marker in the study of leiomyomas. *Science* 150: 67, 1965.
7. Lyon M. F. Gene action in the X chromosome of the mouse (*Mus musculus* L.). *Nature* 190: 372, 1961.

## BOOK REVIEWS

*Tumors of the parathyroid glands Atlas of tumor pathology 2nd series no 14* By Benjamin Castleman and Sanford I. Rosner 96 pages US \$4.50 Armed Forces Institute of Pathology Bethesda Maryland 1978

This volume is the last in the excellent series of monographs treating different problems in tumor pathology. They are all of great interest not only to the professional anatomic pathologists but also contain excellent information regarding recent developments in clinical problems relevant to the subject. The readers of the *Acta Medica Scandinavica* will find interesting facts about such problems as clinical symptoms and epidemiology of hyperparathyroidism beside an atlas of both macro- and microscopic anatomy.

Castleman is without doubt the leading pathologist in this subject and the experience from Massachusetts General Hospital is unique both as regards metabolic surgical and pathological aspects of the disease. The book is profusely illustrated and the pictures are of very high quality. It seems to me that this must be a real goldmine for many specialists who are interested in the field from different points of view.

Of special importance is the discussion about the different types of functional hyperparathyroidism. This problem has been clearly delineated by Castleman in pathology and by the clinicians in Boston. It seems clear that adenoma located in one gland is the cause in about 80% of the patients whereas hyperplasia occurs in practically all the others with about 15% chief cell hyperplasia and about 1-2% hyperplasia of the clear cells. Carcinoma is quite less than 3%. The clinical anatomical findings in different processes are treated and it is evident that they are independent of each other. The facts seem to support the assumption that carcinoma does not arise from adenoma.

Jan G. Waldenström

*Current problems in cancer vol III no 5 Plasma cell neoplasms* By Raymond Alexanian 60 pages \$5.00 Year Book Medical Publishers Chicago and London 1978

During the last years some new series treating current problems and topics in haematology or oncology have been started. It is clear that the frontiers are advancing rapidly in both sciences and it is also evident that they are closely connected. Nobody can contradict the statement that a first rate modern oncologist has to be well versed in haematology to a certain extent this is also true *mutatis mutandis*.

The series regarding cancer problems contains an excellent very short monograph by Alexanian who has devoted his research chiefly to the treatment of multiple myeloma and related problems. There is also a list of current problems that will be treated in forthcoming issues. This list contains a number of important and interesting subjects. It seems to me that this type of information in oncology from the Year Book Publishers and with an editorial board consisting of leading departments of oncology may be of great interest also to the internists. It is evident that oncology will come of ever increasing importance to internal medicine and this small monograph on the plasma cell neoplasms is very well suited for internists.

About half the part on myeloma treats the therapy of this condition and the other half contains an admirably concentrated presentation of the most important diagnostic facts. It is always a pleasure to follow an author who has a real personal experience in the field that he is writing about. Even if the reviewer does not agree on all points regarding the treatment system used by Alexanian, the presentation makes very stimulating reading and is well organized.

Also other plasma cell dyscrasias and gammopathies including Waldenström's macroglobulinemia are very well presented.

Jan G. Waldenström

*British Medical Bulletin The HLA System vol 3 no 3* Edited by W. F. Bodmer 320 pages £5 or \$10.00 Published by The Medical Department The Royal Society of Medicine Council 65 Davies Street London W1P 2AA 1978

This volume of the *British Medical Bulletin* gives a beautiful up-to-date survey of the major human histocompatibility system or complex—the HLA system—as defined by a group of closely linked loci on chromosome no. 6. Contributions to this issue are practically all the best known HLA research people in the United Kingdom.

The volume covers more or less all aspects of the system including serological and cellular typing, its importance in relation to transplantation and the association between the HLA system and various diseases. Immunogenetics and chemistry of the HLA system and its ligands are also covered as are other genetic markers or less closely linked to the 'old' HLA A and B loci.

The volume can be highly recommended for every one interested in the HLA system: clinicians as well as specialized people working with tissue typing. The editor, Walter Bodmer, has as expected secured individual contributions with a high scientific quality.

F. Aissac

## Relationship Between Biochemical and Clinical Features in an English Anderson-Fabry Family

M N Hamers D Wise A Ejtofor A Stryland D Robinson and J M Tager

*From the Laboratory of Biochemistry B C P Jansen Institute University of Amsterdam  
Amsterdam The Netherlands the West Hill Hospital Dartford and the Department  
of Biochemistry Queen Elizabeth College University of London  
London United Kingdom*

**ABSTRACT** The relationship between biochemical parameters and clinical symptoms in angiokeratoma corporis diffusum universale (Anderson Fabry's disease) has been studied in an extensive English family. Biochemical parameters measured were  $\alpha$ -galactosidase activity in urine and in single hair and the urinary glycosphingolipid excretion over 24 h. The clinical symptoms evaluated included occurrence of pain, the prevalence of skin lesions, an abnormal ECG, cornea verticillata and other features. Nine male patients and 13 female carriers were studied. No correlation between biochemical parameters and the severity of the clinical symptoms could be found either in the hemizygotes or in the heterozygotes. The urinary  $\alpha$ -galactosidase activity in all the heterozygotes lay within the normal range. All the obligate heterozygotes (mothers and daughters of hemizygotes) could be detected by analysis of hair roots. Additional heterozygotes were recognized on the basis of clinical symptoms and hair root analysis.

**Key words:** Fabry's disease, lyonisation, heterozygote detection,  $\alpha$ -galactosidase.

Acta Med Scand 206 5 1979

<sup>1</sup> Anderson Fabry's disease, or angiokeratoma corporis diffusum universale, is an inherited metabolic disorder of glycosphingolipid metabolism (30) caused by deficiency of the lysosomal enzyme ceramidetrihexosidase (EC 3.2.1.47), an  $\alpha$ -galactosidase (17, 27). Whereas two  $\alpha$ -galactosidase isoenzymes, A and B, are present in normal tissue, the former is absent in Fabry's disease (4, 23). The latter enzyme has recently been identified as N-acetyl- $\alpha$ -galactosaminidase, which has some activity towards substrates containing a terminal  $\alpha$ -ga-

lactosidic moiety (7, 28). Thus, the B isoenzyme has no relation to Anderson Fabry's disease.

The enzymic defect in Anderson Fabry's disease results in progressive accumulation of galactosyl ( $\alpha$  1 $\rightarrow$ 4) galactosyl ( $\beta$  1 $\rightarrow$ 4) glucosylceramide (ceramidetrihexoside or ceramide 3, abbreviated as CTH or GL 3) in most tissues of the body, especially in kidney (26) and the cardiovascular system (6), but also in liver (26, 31), spleen (26, 31), pancreas (26) and ganglion cells of the peripheral nervous system (26). Increased concentrations of GL 3 are also found in urinary sediment (8, 31) and plasma (5, 33). A second glycosphingolipid, galactosyl ( $\alpha$  1 $\rightarrow$ 4) galactosylceramide (digalactosylceramide or ceramide 2b, abbreviated as GL 2b), is found in elevated concentrations in kidney (31), urinary sediment (8, 31) and pancreas (26).

The clinical features are of various kinds (18, 31, 35). In the skin there are numerous small, very dark red punctate or hemispherical papules which are sometimes a few mm in diameter but often so small as to be difficult to detect. The skin lesions may be one of the earliest manifestations and may lead to diagnosis in childhood. Another typical feature is the intermittent pain in the extremities which is often induced by changes in environmental temperature. Progressive accumulation of glycolipids in the kidneys results in renal impairment, with gradual deterioration of renal function resulting commonly in death at the ages of 30-60. As a consequence of the systemic vascular involvement, tortuous retinal

**Abbreviations:** GL 3 = ceramidetrihexoside; GL 2b = digalactosylceramide or ceramide 2b; CR = cross reacting immunological; C = cardiogram.



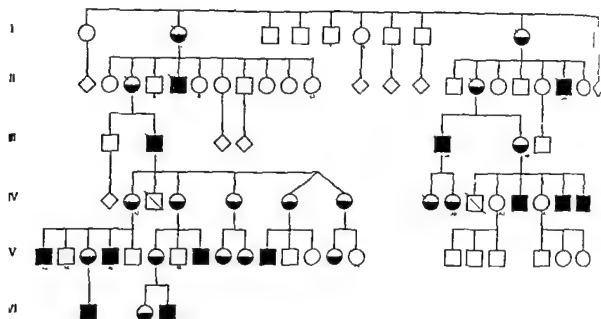


Fig. 1 Pedigree of the family  $\bullet$  = Heterozygote  $\blacksquare$  = hemizygote  $\diagdown$  = deceased  $\diamond$  = unaffected offspring

veins are a common feature. Cornea verticillata is also present in most affected adults. Other features of the disease include oedema, colitis, cerebral vascular disturbances in early adult life, cardiac enlargement and ECG abnormalities with or without hypertension, aortic valve disease, arthritis, varicose veins, necrosis of the head of the femur, nail dystrophy and pale nail beds.

Deficiency of  $\alpha$ -galactosidase A is inherited in a linked fashion (14, 15, 20, 35). Thus the male patients are hemizygotes and the mothers and daughters of the male patients are obligate heterozygotes. In females heterozygous for the Fabry trait, the amount of  $\alpha$ -galactosidase activity in the somatic cells will depend on whether the normal or the affected X-chromosome is expressed in these cells, the other X-chromosome being inactivated (19). The inactivation of one of the X-chromosomes in the somatic cells of females (lyonization) occurs in a random way in an early stage of embryonic development (19). Ropers et al. (25) in contrast suggest that inactivation of the X-chromosome in heterozygotes for the Anderson-Fabry trait is not a random process but is influenced by the genotype. However, we have found that the expression of  $\alpha$ -galactosidase A differs in monozygous twins (IV-17 and IV-19) in the English family and in a Dutch family (22); this shows that

the inactivation is not affected by the genotype. Whereas in the hemizygotes  $\alpha$ -galactosidase activity is absent, in the heterozygotes a broad spectrum of activities is found (9). The question arises of the relationship between the amount of enzyme activity present in an individual, the amount of glycosphingolipids accumulated and the severity of the clinical symptoms. However, measurement of the amount of  $\alpha$ -galactosidase activity in biopsies from heterozygotes can be misleading as intermingling of cells positive or negative for  $\alpha$ -galactosidase A no longer occurs after lyonization has taken place at a certain stage of tissue development. This causes the formation of patches of cells of clonal origin (11, 12). Consequently, cellular material of heterozygotes may consist entirely of normal (or defective) cells depending on the site of the biopsy in relation to the size of the patches. To circumvent this drawback, the relationship between urinary  $\alpha$ -galactosidase activity and the amount of urinary glycosphingolipids was studied because the enzyme activity as well as the glycosphingolipids in urine are derived mainly from the kidneys (3, 8). Another possibility to circumvent the above problem is the use of cellular material derived from a source with a known number of primordial cells and a known size of the patches. This is the case with hair roots, which originate

om only a few cells at the time of lysis and  
arm patches on the scalp of about 0.004–0.021 mm<sup>2</sup>

In this paper the relationship between the level  
of  $\alpha$  galactosidase A activity, the amount of gly-  
cosphingolipids excreted in the urine and the  
severity of the clinical symptoms was investigated  
in hemizygotes and heterozygotes in a single Eng-  
lish Anderson Fabry family.  $\alpha$  Galactosidase ac-  
tivity was measured in urine and in single hair roots  
plucked from different areas of the scalp.

## SUBJECTS AND METHODS

All persons studied were members of a single extensive  
Anderson Fabry family (Fig. 1) first described by John-  
ston et al. (16) whose original code has been maintained.  
The deceased patients (II 2, 19, II 5, II 7, II 32, II 36,  
II 12 and III 38) have been described by Johnston et al.  
None of the individuals studied had renal failure.

Collection of 24-hour urine was started in the morning  
in plastic bottles without any preservatives. The next  
morning the urines were collected and centrifuged for 30  
min at 22 000  $\times$ g within 6 hours after collection. The sedi-  
ment was freeze-dried and stored at -20°C until further  
use. Portions of 100 ml of the supernatant were processed  
and the ratio of  $\beta$  hexosaminidase to  $\alpha$ -galactosidase was  
determined exactly as described by Rietra et al. (24). The  
whole supernatant from patients IV 41 and V 13 was pro-  
cessed and used for detecting whether cross reacting im-  
munological material (CRIM) was present exactly accord-  
ing to Rietra et al. (23). The freeze-dried urinary sedi-  
ments were processed essentially as described by Vance  
and Sweetley (34) and GL 3 and GL 2b were measured  
gaschromatographically according to the method of  
Sweetley and Tao (32). Less than 24-hour urine portions  
were obtained from some of the children. In such cases a  
semiquantitative glycosphingolipid analysis was carried  
out using thin layer chromatography according to Vance  
and Sweetley (34). With this method no glycosphingolipids  
can be detected in 100-ml portion of urine from a healthy  
control.

Hair roots plucked by hand from different areas of  
the scalp were classified as normal heterozygous or  
hemizygous (9). Total  $\alpha$  galactosidase and  $\beta$  hexos-  
aminidase activities were measured as described by  
Ejofors et al. (9).

The severity of pain was expressed in categories vary-  
ing from absent (-) to very severe (+++). The other  
clinical features were evaluated as absent (-) or present  
(+).

## RESULTS AND DISCUSSION

The results of the investigations are listed in Ta-  
ble I.

**Hemizygotes.** Patient V 16 now lives in Denmark.  
His hair roots were collected in Denmark by Dr F

Svendstrup transported by air to London and as-  
sayed there. No other biochemical parameters were  
measured in this patient. From patients VI 1 and  
VI 3 who were too young for 24-hour urine to be  
collected without special equipment, very small  
samples were collected just enough to measure the  
urinary enzyme ratio for diagnosis. From patient  
VI 3 it was impossible to collect hair roots because  
the hairs were too fragile to pull out the roots.

The urinary ratio  $\beta$  hexosaminidase/ $\alpha$  galacto-  
sidase in all the hemizygotes was  $>40$  as expect-  
ed. All the hair roots could be classified as hemi-  
zygous or occasionally as heterozygous. Table I  
clearly shows that the clinical symptoms in the  
hemizygotes are variable even among patients of  
similar age. The same conclusion was drawn by  
Van den Bergh (2) in a study of the clinical symp-  
toms of 50 hemizygotes described in the literature.  
Because all hemizygotes studied here belong to one  
and the same family, they must have the same ge-  
notype for  $\alpha$  galactosidase A, thus the variability of  
the clinical symptoms must be explained in terms  
of the rest of the genotype and/or environmental  
factors. Another parameter that can be measured  
more accurately than the clinical symptoms is the  
glycosphingolipid excretion, but again a variability  
is found which is related neither to age nor to the  
clinical features.

**Obligate heterozygotes.** Although the urinary  $\beta$   
hexosaminidase/ $\alpha$  galactosidase ratio lay within the  
normal range ( $<20$ ), the subjects could all be clas-  
sified as heterozygotes on the basis of the hair root  
analyses, a large number of which showed hemi-  
zygous values (9).

**Other heterozygotes.** An additional number of  
subjects who are not obligate heterozygotes were  
also detected by means of the hair root analysis.

In the heterozygotes too there does not always  
seem to be a clear correlation between the bio-  
chemical parameters and the clinical symptoms.  
For instance, patient III 39 has a reasonable amount  
of  $\alpha$  galactosidase, as may be concluded from the  
large proportion of normal hair roots, and excretes  
indeed very little GL-3 and GL-2b, but shows  
nevertheless clear clinical symptoms. On the other  
hand, patients IV 10, IV 19 and V 22 all show in-  
creased GL-3 and GL-2b excretion, as well as clinical  
symptoms, findings that may be correlated with  
the fact that they have low  $\alpha$  galactosidase activity.  
To judge from the large proportion of hemizygous  
hair roots, Patient V 18 has the highest excretion of

Table 1 Biochemical parameters and clinical symptoms in members of an Anderson Fabry family

N=normal Het=heterozygous Hem=hemizygous classified on the basis of the  $\alpha$ -galactosidase activity in relation to the  $\beta$ -hexosaminidase activity N D=not determined

Subject	Urinary ratio $\beta$ -hexosaminidase/ $\alpha$ -galactosidase*		No. of hair roots classified as				Glycosphingolipids in urinary sediment ( $\mu$ mol/24-h urine)		Clinical features				
	Age (y)		N	Het	Hem	Total	GL 3 <sup>b</sup>	GL 2b <sup>c</sup>	Pain	Skin lesions	Abnormal ECG	Cornea verticillata	Other
<b>Hemizygotes</b>													
IV-41	38	<0	0	0	17	17	0.918	0.268	+	+	+	+	Angina pectoris
IV-43	29	93	0	0	10	10	1.248	0.122	+	+	-	+	Diffuse leukodystrophy
IV-44	20	63	0	0	16	16	2.519	0.453	+	+	-	+	
V-13	32	160	0	0	10	10	0.791	0.169	+++	+	-	+	Slow growth, 160 cm, few fingers, oedema
IV-16	25	N D	0	0	6	6	N D	N D	+++	+	-	+	
V-20	17	1.0	0	2	9	11	0.954	0.241	++	+	-	+	Slow growth
V-23	15	79	0	2	8	10	0.941	0.024	+	+	-	+	Haematuria
V-11	2	97	0	0	4	4	N D	N D	-	-	-	N D	
V-13	1	127			N D		N D	N D	N D	+	N D	N D	
<b>Oblique heterozygotes</b>													
III-39	66	9.0	11	3	2	16	0.051	0.013	+	-	-	+	
IV-10	53	8.3	0	8	8	16	0.155	0.056	+	+	+	+	
IV-13	43	8.5	1	5	5	11	0.098	0.016	+	+	+	+	
IV-15	38	7.7	2	7	4	13	0.050	0.016	-	-	-	-	Tortuous retinal veins
IV-17	36	7.6	8	2	1	11	0.020	Trace	-	-	-	-	
IV-19	36	11	1	4	9	14	0.145	0.037	-	+	-	+	
IV-38	44	16	2	3	12	17	0.022	Trace	++	-	+	+	Fever, nodular vasculitis, proteinuria, oedema
V-16	28	2.7	1	5	3	9	0.044	Trace	+	-	-	N D	
	22	14	5	3	3	11	0.270	0.084	-	+	-	+	
<b>Trace heterozygotes</b>													
	21	4.8	5	5	6	16	0.082	Trace	-	+	-	-	
	19	13	2	4	9	15	0.110	Trace	++	+	-	+	
	9	5.7	4	6	6	16	0.032	Trace	-	-	-	-	
12	3	6.4	7	4	3	14	Present <sup>d</sup>		-	-	-	-	
<b>Other family members</b>													
V-24 (o)	13	5.5			N D		Not detectable		-	-	N D	-	
V-25 (f)	11	6.8	9	0	0	9	Not detectable <sup>e</sup>		-	-	N D	-	
V-27 (f)	8	6.2	8	3	0	11	0.022	Trace	-	-	N D	-	

\*  $<20$  in normal individuals,  $>40$  in hemizygotes (22)

<sup>b</sup> Mean value in normal individuals is 0.025 and the range reported for hemizygotes is 0.120-4.91 (2)

<sup>c</sup> Trace amounts are found in normal individuals and trace amounts up to 0.86  $\mu$ mol/24-h urine in Fabry hemizygotes

<sup>d</sup> Detected in thin-layer chromatograms of material from 70 ml and 137 ml urine

<sup>e</sup> Thin-layer chromatogram of material from 130 ml urine

<sup>f</sup> Thin-layer chromatograms of material from 84 ml and 120 ml urine

GL 3 and GL 2b found among the heterozygotes although from the hair root analysis it seems that she has an intermediate  $\alpha$ -galactosidase activity. Even more surprising is the observation in patient IV-38 who has a large proportion of defective hair

roots and much pain but excretes very little if at all GL 3 or GL 2b. In contrast patient IV-17 has a very large proportion of normal hair roots, no clinical symptoms and no abnormal glycosphingolipid excretion. The latter finding has been reported by

fore (1-21). The opposite type of carrier with very low  $\alpha$  galactosidase activity as indicated by analysis of urine, plasma and leukocytes has been reported by Ruetra et al. (22) (carrier M. K. whose urinary  $\beta$  hexosaminidase/ $\alpha$  galactosidase ratio was  $\approx 100$ ). We were able to perform a glycosphingolipid analysis of 24-hour urine from this carrier: the amount of GL 3 excreted per 24 hours was 1.79  $\mu$ moles and that of GL 2b 0.66  $\mu$ moles. Thus the amount of glycosphingolipids excreted by M. K. is comparable to that excreted by hemizygotes. Moreover M. K. has severe clinical symptoms (W. P. de Groot, personal communication). Thus there seems to be a good correlation between the expression of  $\alpha$  galactosidase A and the other parameters in this case.

**Three other family members** The boy (V-24) could be diagnosed as normal and neither of the girls (V-25 and V-27) could be diagnosed as heterozygotes.

Another conclusion that can be drawn from these results is that although determination of the urinary enzyme ratio is a good method of diagnosing hemizygotes, especially if they are babies and have no clinical symptoms, the diagnosis of heterozygotes by this method is not always possible owing to the wide range of normal ratios. Indeed, the urinary  $\beta$  hexosaminidase/ $\alpha$  galactosidase ratios in all of the heterozygotes in this English family lay within the normal range (Table I). Much less overlap between the distribution of  $\alpha$  galactosidase activity in normal persons and Fabry heterozygotes is found in the  $\alpha$  galactosidase levels in hair roots (9-13-29) and this is a very good method for diagnosis of heterozygotes. However, the combination of the hair root analysis with the measurement of glycosphingolipid excretion and the clinical diagnosis is the most reliable method.

The general conclusion of this study is that there is no clear correlation between the expression of  $\alpha$  galactosidase A (i.e. the amount of  $\alpha$  galactosidase activity present) and the biochemical or clinical features, with the possible exception of the very mildly and severely affected carriers. Obviously other factors, such as the complete genotype of the subject, play an important role in determining the expression of the clinical symptoms and the course of the disease. Furthermore, as a consequence of the lyonisation phenomenon, it is impossible to prove conclusively that a female member of a Fabry family who has a heterozygous

mother is not heterozygous herself. It is in theory possible that inactivation of one of the X-chromosomes has occurred in such a way that the unaffected X-chromosome is expressed in all somatic cells, so that the  $\alpha$  galactosidase activity is completely normal. Thus since it is difficult if not at present impossible to establish with absolute certainty that a female member of an Anderson Fabry family is not heterozygous for the trait, all pregnancies in the family must be considered at risk. However, prenatal diagnosis of Anderson Fabry disease is possible (5-10).

Finally, it should be noted that no CRIM could be detected in the urine of two hemizygotes from the English family (IV-41 and V-13). The absence of CRIM has also been established in two American patients (4), in a Dutch (23), an Italian, an Irish and a French patient (Hamers, unpublished observations). Thus there is no indication as yet of genetic heterogeneity in Anderson Fabry's disease.

## ACKNOWLEDGEMENTS

This study was supported by grants from the Prevento Fund, the National Kidney Research Fund (UK) and the Netherlands Organization for the Advancement of Pure Research, under auspices of the Netherlands Foundation for Fundamental Medical Research and a Young Visito Grant (M. N. Hamers) from the British Council.

## REFERENCES

- Avila J. L., Convit J. & Velasquez Avila G. Br J Dermatol 89: 149, 1973.
- Van den Bergh F. A. J. T. M. Biochemical studies on Fabry's disease. pp. 86-89. Ph.D. thesis University of Amsterdam. Knips Repro. Meppel 1978.
- Van den Bergh F. A. J. T. M., Ruetra P. J. G. M., Kolk Vegter A. J., Bosch E. & Tager J. M. Acta Med Scand 200: 249, 1976.
- Beutler E. & Kuhl W. Nature 239: 207, 1972.
- Brady R. O., Uhlendorf B. W. & Jacobsen C. B. Science 172: 174, 1971.
- Christensen Lou H. O. Acta Pathol Microbiol Scand 68: 332, 1966.
- Dean K. J., Sung S. S. J. & Sweeley C. C. Biochem Biophys Res Commun 77: 1411, 1977.
- Desnick R. J., Sweeley C. C. & Knivt W. J. Lipid Res 11: 31, 1970.
- Ejlofor A., Robinson D., Wise D., Hamers M. N. & Tager J. M. In: Enzymes of lipid metabolism (ed. S. Gatt, L. Freysz and P. Mandel). Advances in experimental medicine and biology, vol. 101, pp. 719-725. Plenum Press, New York, 1978.
- Gallaard H., Niermeijer M. F., Hahnemann N., Mohr J. & Sørensen S. A. Clin Genet 5: 368, 1974.

- 1 Gartler S M Gandini E Angioni G & Argiolas N *Ann Human Genet* 33 171 1969
- 2 Gartler S M Gandini E Hutchinson M T Campbell B & Zechlin G *Ann Human Genet* 35 1 1971
- 3 Grimm T Wienker T F & Ropers H H *Human Genet* 32 329 1976
- 4 Grzeschik K H Grzeschik A M Banhof S Romeo G Siniscalco M Van Someren H Meera Khan P Westerveld A & Bootsma D *Nature* 240 48 1972
- 5 Hamers M N Westerveld A Meera Khan P & Tager J M *Human Genet* 36 289 1977
- 6 Johnston A W Waarland B J & Weller S D V *Ann Human Genet* 30 25 1966
- 7 Kint J A *Science* 167 1268 1970
- 8 Kint J A & Carton D In *Lysosomes and storage diseases* (ed H G Hers and F van Hoof) pp 357-380 Academic Press New York 1973
- 9 Lyon M F *Biol Rev* 47 1 1972
- 10 Opitz J M Stiles F C Wise D Race R R Sanger R Von Gemmingen G R Kierland R R Cross E C & De Groot W P *Am J Human Genet* 17 325 1965
- 11 Philippart M Sarlieve L & Manacorda A *Pediatrics* 43 201 1969
- 12 Rietra P J G M Brouwer Kelder E M De Groot W P & Tager J M *J Mol Med* 1 237 1976
- 13 Rietra P J G M Molenaar J L Hamers M N Tager J M & Borst P *Eur J Biochem* 46 89 1974
- 14 Rietra P J G M Tager J M & De Groot W P *Chin Chim Acta* 40 229 1972
- 15 Ropers H H Wienker T F Grimm T F ter K & Bender K *Am J Human Genet* 29 30 1977
- 16 Schibanoff J M Kamoshita S & O'Brien J S *Lipid Res* 10 515 1969
- 17 Schram A W Hamers M N Brouwer Kelder E Donker Koopman W E & Tager J M *Bioch Biophys Acta* 482 125 1977
- 18 Schram A W Hamers M N & Tager J M *Biochim Biophys Acta* 482 138 1977
- 19 Spence M W Goldbloom A L Burgess J J D Entremont D Ripley B A & Weldon K L *Med Genet* 14 91 1977
- 20 Sweeley C C & Klionsky B *J Biol Chem* 238 3149 1963
- 21 Sweeley C C Klionsky B Krivit W & Desnick R J In *The metabolic basis of inherited disease* (J B Stanbury J B Wyngarden and D S F denckson) pp 663-687 McGraw-Hill New York 1972
- 22 Sweeley C C & Tao R V P In *Methods carbohydrate chemistry* (ed R L Whistler and J L Bemiller) vol 6 pp 8-13 Academic Press New York 1972
- 23 Vance D E Krivit W & Sweeley C C *J Lipid Res* 10 188 1969
- 24 Vance D E & Sweeley C C *J Lipid Res* 8 6 1967
- 25 Wise D Wallace H J & Jelinek E H *Q J Med* 31 177 1962

## T<sub>4</sub>, T<sub>3</sub> and Reverse-T<sub>3</sub> Determinations in Connection with the TRH test in the Evaluation of Possible Hyperthyroidism

Gunnar Kallner and Jan Gustaf Ljunggren

*From Department of Medicine II Södersjukhuset and Department of Medicine  
St Goran's Hospital Stockholm Sweden*

**ABSTRACT** One disadvantage of the TRH test is that an absent or blunted TSH response is seen not only in hyperthyroid patients but also in some normal subjects. The aim of the present study was to elucidate whether the discriminatory power between eu and hyperthyroidism could be increased by determining the T<sub>3</sub> and T<sub>4</sub> levels before and after the TRH administration. The study population consists of 30 patients referred for evaluation of suspected hyperthyroidism. The results show that all but one of the patients ( $n=20$ ) who had T<sub>3</sub> levels within the normal reference limits increased these levels after TRH administration, whether their TSH response was normal or blunted. One patient's T<sub>3</sub> levels decreased after TRH. All the patients ( $n=10$ ) who had T<sub>3</sub> levels within the hyperthyroid range showed a decrease after TRH. The decrease was significantly correlated ( $r=0.90$ ) to the magnitude of the increase. No consistent T<sub>4</sub> and no change in reverse T<sub>3</sub> response was obtained. The addition of T<sub>3</sub>, T<sub>4</sub> or reverse-T<sub>3</sub> determinations in connection with the TRH test does not seem to increase the discriminatory power of the test.

**Key words** thyroxine triiodothyronine reverse triiodothyronine TRH test hyperthyroidism

Acta Med Scand 206 11 1979

The recent development of radioimmunoassay techniques for the estimation of thyroid hormones and thyroid stimulating hormone (TSH) has provided a sufficiently sensitive and simple means of directly quantitating these substances in the serum in both normal and pathological states.

The clinical value of TSH determinations is now well recognized in the diagnosis of primary hypothyroidism (7). In fact the discriminatory power of TSH determination is so good that a normal TSH level excludes primary hypothyroidism. In the labo-

ratory discrimination between eu and hyperthyroidism the determination of 3,5,3'-triiodothyronine (T<sub>3</sub>) seems to be superior to thyroxine (T<sub>4</sub>) determination even when corrections are made for variations in the hormone binding serum proteins (8, 14). The discriminatory power of T<sub>3</sub> determinations is also higher than the thyrotropin releasing hormone (TRH) test even though a normal TSH response to TRH stimulation excludes hyperthyroidism (13). One disadvantage of the TRH test is that an absent or blunted TSH response is seen not only in hyperthyroid patients but also in some normal subjects (9, 14). The reason for an absent or blunted response in normal individuals is unclear.

It has recently been claimed that determination of T<sub>3</sub> and T<sub>4</sub> levels is of value as a complement to the TRH test (1, 2, 4, 11). The aim of the present investigation was to elucidate whether the discriminatory power of the TRH test could be increased by the additional determinations of T<sub>3</sub>, reverse T<sub>3</sub> (3,3',5'-triiodothyronine) and T<sub>4</sub> levels. Special reference was made to euthyroid subjects demonstrating an abolished or blunted TSH response. An increase in T<sub>3</sub> or T<sub>4</sub> levels despite an absent or blunted TSH response may be found if the sensitivity of the assay methods is higher for T<sub>3</sub> and T<sub>4</sub> than for TSH.

### PATIENTS AND METHODS

Thirty patients referred for evaluation as suspect hyperthyroidism were included in the study. Five were men with a mean age ( $\pm$  S.D.) of  $44 \pm 10$  years (range 29-54).

**Abbreviations** TSH = thyroid stimulating hormone; TRH = thyrotropin releasing hormone; T<sub>3</sub> = 3,5,3'-triiodothyronine; reverse T<sub>3</sub> = 3,3',5'-triiodothyronine; T<sub>4</sub> = thyroxine.

Table I Serum levels of  $T_4$ ,  $T_3$  and reverse  $T_3$  in the three groups

	Group 1			Group 2			Group 3		
	0	120	180	0	120	180	0	120	180
$T_4$									
$\bar{x}$	76.6	85.6	86.9	173.5	169.0	176.3	86.9	91.3	89.3
$\pm$ S.E.	5.8	6.6	6.5	17.0	17.0	17.6	8.2	8.6	7.7
		*			N.S.	N.S.		N.S.	N.S.
$T_3$									
$\bar{x}$	1.75	2.23	2.04	4.82	4.12	4.07	1.93	2.15	2.14
$\pm$ S.E.	0.14	0.14	0.15	0.65	0.50	0.46	0.11	0.09	0.18
		**	***		***	**		**	N.S.
Reverse $T_3$									
$\bar{x}$	0.20	0.23	0.22	1.38	1.40	1.38	0.35	0.31	0.32
$\pm$ S.E.	0.03	0.02	0.02	0.34	0.39	0.37	0.06	0.04	0.05
		N.S.	N.S.		N.S.	N.S.		N.S.	N.S.

N.S. = Not significant \*  $0.01 < p < 0.05$  \*\*  $0.001 < p < 0.01$  \*\*\*  $p < 0.001$ 

The mean age ( $\pm$  S.D.) of the women was  $56 \pm 14$  years (range 21–76). Each patient underwent a full clinical investigation. Thyroid function tests included estimation of  $T_4$ ,  $T_3$ , reverse  $T_3$  and TSH levels as well as the TRH test,  $T_4$  suppression test and scintiscans.

$T_4$  and  $T_3$  were determined by radioimmunoassay as previously described (10). The reference value in serum (mean  $\pm$  S.D.) for  $T_4$  is  $89 \pm 17$  for  $T_3$   $1.77 \pm 0.34$  nmol/l.

Reverse  $T_3$  was determined using a commercially available kit (Hypolab, Comins, Switzerland). The normal serum level (mean  $\pm$  S.D.) is  $0.34 \pm 0.20$  nmol/l.

Serum TSH was determined with a commercial kit ebas TSH test Pharmacia Diagnostics, Uppsala). The reference limit for men is  $< 7.2$  and for  $< 5.5$   $\mu$ U/ml.

TRH test was performed on an out patient basis  $100 \mu$ g synthetic TRH (Hoffman La Roche, Basel, Switzerland) administered intravenously. Serum samples were drawn before and at 20 and 60 after the injection for TSH analysis and at 120 and 180 after the injection for  $T_4$ ,  $T_3$  and reverse  $T_3$  determinations. A TSH increment of more than  $3.0 \mu$ U/ml during the first hour is regarded as a normal response (14).

The  $T_4$  suppression test and scintiscans were performed according to standard procedures (16). Three mg of l thyroxine was given orally as a single dose.

## RESULTS

The results of the complete clinical and laboratory evaluation showed that the patients could be divided into three groups. Group 1 comprised 10 patients with total evidence of normal thyroid function. Group 2 comprised 10 patients with total evidence of hyperthyroidism. Group 3 comprised 10 patients in whom a definite diagnosis of a disease of

thyroid function could not be made by the clinical investigation alone and in whom the basal  $T_3$ , reverse  $T_3$  and  $T_4$  levels were within the reference interval despite an impaired TSH response to TRH.

**Group 1** Eight of the 10 patients in this group were women. The age range was 23–65 years (mean  $43.6$ ). All were clinically euthyroid. All basal  $T_4$  and reverse  $T_3$  levels were within the reference limit (mean  $\pm$  2 S.D.) and the TSH response to TRH was normal (increment  $> 3.0 \mu$ U/ml) in all subjects. The TSH increment was  $8.28 \pm 1.71 \mu$ U (mean  $\pm$  S.E.). The results are shown in Table I.

All patients showed increased levels of  $T_3$  at TRH. A highly significant ( $p < 0.001$ ) increase in levels was obtained after both 120 28.8% and 180 16.9% in the whole group. No significant change was observed in reverse  $T_3$  levels at TRH.

Eight patients showed increased levels of  $T_4$  at TRH. decreased values were seen in two ( $< 1$  nmol/l in both). A significant increase in  $T_4$  level was obtained in the whole group both after 120 12.8% ( $0.01 < p < 0.05$ ) and after 180 14.7% ( $0.001 < p < 0.01$ ).

Thus in this group of patients with apparent normal thyroid function and normal TSH response to TRH an increase in  $T_3$  was obtained in all patients after 120 and 180. Only 8 of the 10 patients also showed an increase in  $T_4$  levels. No change in reverse  $T_3$  was seen.

**Group 2** Eight of the 10 patients in this group were women. The age range was 46–73 years (mean

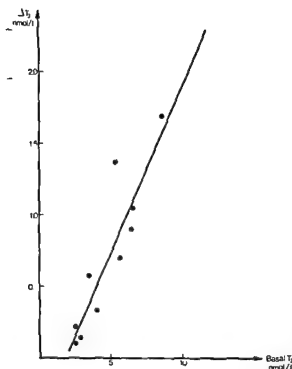


Fig 1 Decrease in  $T_3$  levels after TRH administration in the hyperthyroid patients (group 2)

All had clinical signs and symptoms of hyperthyroidism. All basal  $T_4$  and  $T_3$  levels and all but two reverse  $T_3$  values were within the hyperthyroid range. All patients had an abolished TSH response to TRH. The results are shown in Table I.

All patients showed decreased  $T_3$  levels after TRH. A significant decrease in  $T_3$  levels for the whole group was obtained after 120 min (13.0% ( $p < 0.001$ )) and after 180 min (13.3% ( $0.001 < p < 0.01$ )). The decrease was significantly correlated to the basal  $T_3$  levels ( $r = 0.90$ ) as shown in Fig 1.

No significant changes in reverse  $T_3$  or  $T_4$  levels were obtained in this group.

Thus, in this group of hyperthyroid patients a decrease in  $T_3$  levels was obtained in all patients both after 120 and after 180 min. No significant change in reverse  $T_3$  or  $T_4$  levels was seen.

**Group 3** Nine of the 10 patients in this group were women. The age range was 45–76 years (mean 60.2). The state of the thyroid function could not be settled by the clinical examination alone. All basal  $T_3$ , reverse  $T_3$  and  $T_4$  levels were within the reference limit ( $\pm 2$  S.D.). Three of the patients had an abolished TSH response to TRH, the response in

seven was blunted ( $0 < \text{increment} < 3.0 \mu\text{U}/\text{m}$ ). The results are shown in Table I.

Four of the 10 patients had a normal radioiodine uptake test and a normal  $T_4$  suppression test. T scintiscans revealed no autonomously functioning nodule, thus fulfilling our criteria for a normal thyroid function. All four patients showed increased levels of  $T_3$  after TRH. The mean increase was 15.9% at 120 min and 22.1% at 180 min. No consistent response was obtained.

Another four of the 10 patients had abnormal suppression tests and scintiscans indicating autonomously functioning nodules. Three patients showed increased levels of  $T_3$  after TRH and one decreased level. The mean increase was 25.8% at 120 min and 16.6% at 180 min. No consistent  $T_4$  response was obtained.

The remaining two patients had both been previously operated upon for toxic nodular goiters. The 24-hour radioiodine uptake tests were 51% and 46% respectively. For technical reasons no  $T_4$  suppression test could be performed. Both patients showed increased levels of  $T_3$  after TRH. No significant change was seen in reverse  $T_3$  levels after TRH.

Thus, the results show that all but one patient with normal basal levels of  $T_3$  increase these levels after TRH administration despite blunted or abolished TSH responses and autonomously functioning thyroid nodules.

## DISCUSSION

The present results indicate that patients with normal basal levels of  $T_3$  significantly increase these levels 120 and 180 min after TRH administration regardless of a normal, blunted or abolished TSH increase. The increase in  $T_3$  levels seen in normals is consistent with the findings of previous investigators (1, 3, 6, 11, 13, 15). The observation of an increase in  $T_3$  levels despite an abolished or blunted TSH response is both in accordance and in contrast to previous reports (5, 12). Dige-Pedersen and Hummer (5) found that the  $T_3$  response to TRH was significantly correlated with the TSH increase both in normal subjects and in patients with non-toxic goiter, while Sawin and Hershman (12) reported that there was no correlation between the rise in serum TSH and  $T_3$  levels. The finding of an increase in  $T_3$  levels despite an abolished or blunted TSH increase might have to do with a low sensitivity



ry of the TSH assay technique. However, further studies with five different commercially available TSH radioimmunoassay kits generally used in clinical practice yielded similar TSH results (unpublished observation).

The present results also show that all patients with basal levels of  $T_3$  within the hyperthyroid range demonstrate a reduction in these levels after TRH administration. The decrease was significantly correlated to the magnitude of the basal level. Similar findings do not seem to have been reported previously. The mechanism behind the decrease is so far unknown. The results thus indicate that the determination of  $T_3$  levels as a complement to TSH determinations is of no major diagnostic value for the discrimination between eu- and hyperthyroidism. This conclusion can be drawn on the basis that an increase in  $T_3$  levels was obtained in all patients with normal  $T_3$  levels and a decrease was demonstrated in all patients with  $T_3$  levels within the hyperthyroid range. Thus, the determination of the basal  $T_3$  levels alone is sufficient. The inconsistent  $T_4$  response and the absent reverse- $T_3$  response indicate that the determination of these parameters is of no additional diagnostic value as a complement to the TRH test for discrimination between eu- and hyperthyroidism.

In conclusion, the determination of  $T_3$ , reverse  $T_3$  and  $T_4$  levels in addition to the determination of SH after TRH administration does not increase the discriminatory power of the TRH test in the diagnosis of eu- or hyperthyroidism.

#### ACKNOWLEDGEMENTS

This investigation was supported by grants from the Swedish Medical Research Council (No. B 79:19X-02442/12) and the Karolinska Institute.

#### REFERENCES

- Azziz F, Vagenakis A G, Portnay G J, Rapaport B, Ingbar S H & Braverman L E. Pituitary thyroid responsiveness to intramuscular thyrotropin-releasing hormone based on analyses of serum thyroxine, triiodothyronine and thyrotropin concentrations. *N Engl J Med* 292: 273, 1975.
- Burger H G & Patel Y C. Thyrotrophin releasing hormone—TSH. *Clin Endocrinol Metab* 6: 183.
- Chopra I J, Ho R S & Law R. An improved radioimmunoassay of triiodothyronine in serum: applicator to clinical and physiological studies. *J Clin Med* 80: 729, 1972.
- Dige Pedersen H & Hummer L. TRH test. *Ugeskr Laeger* 136: 1351, 1974.
- Serum thyrotropin concentrations under different conditions and after stimulation with thyrotropin-releasing hormone in idiopathic non-toxic goiter. *J Endocrinol Metab* 44: 1115, 1977.
- Faber J, Friis T, Kirkegaard C, Lauridsen B, Nerup J, Rogowski P & Siersbaek Nielsen. Thyroid hormone response to varying doses of TRH. *Acta Endocrinol* 83: 737, 1976.
- Hall R. The immunoassay of thyroid stimulating hormone and its clinical applications. *Clin Endocrinol* 1: 115, 1972.
- Kallner G, Agedal B, Ljunggren J-G & Thulius M. Clinical value of total  $T_4$  and  $T_3$  determinations in patients with suspected hyperthyroidism before and after correction for binding proteins. *Acta Scand* 204: 369, 1978.
- Kaplan M M & Unger R D. Diagnosis of hyperthyroidism. *Clin Endocrinol Metab* 7: 1109, 1976.
- Ljunggren J G, Persson B & Tryselius M. Simultaneous radioimmunoassay for the triiodothyronine and thyroxine in unextracted human serum. *Acta Endocrinol (Kbh)* 81: 487, 1976.
- Patel Y C & Burger H G. Serum triiodothyronine in health and disease. *Clin Endocrinol* 2: 339, 1971.
- Sawin T S & Hershman J M. The TSH response to thyrotropin-releasing hormone (TRH) in young adult men: intra-individual variation and relation to basal serum TSH and thyroid hormones. *J Clin Endocrinol Metab* 42: 809, 1976.
- Shenkman L, Suphavi A, Mitsuma T & Herder C S. Triiodothyronine and thyroid stimulating hormone response to thyrotropin-releasing hormone. *Lancet* 2: 111, 1972.
- Tryselius M, Kallner G & Ljunggren J G. Comparison between serum thyroxine and triiodothyronine estimation and the TRH test in the routine diagnosis of hyperthyroidism. *Acta Med Scand* 201: 1977.
- Uller R P, van Herle A J & Chopra I J. Comparison of alterations in circulating thyroglobulin, triiodothyronine and thyroxine in response to exogenous (bovine) and endogenous (human) thyrotropin. *J Endocrinol Metab* 37: 741, 1973.
- Wallack M S, Adelberg H M & Nicoloff J T. Thyroid suppression test using a single dose of thyroxine. *N Engl J Med* 283: 402, 1970.

## Function of Pituitary-Thyroid Axis after Surgical Treatment of Non-Toxic Nodular Goitre

M. Blichert Toft, J. Egedorf, C. Christiansen and C. K. Axelsson

*From Surgical Department D and the Department of Clinical Chemistry,  
Glostrup Hospital, Copenhagen, Denmark*

**ABSTRACT** Fifty consecutive patients with benign euthyroid nodular goitre underwent goitre resection. In uninodular goitres a remnant of normal thyroid tissue was left, while in multinodular goitres the remnant presented varying degrees of nodularity. The pituitary thyroid function was determined before operation and 3, 6, and 12 months after surgical treatment by measuring serum  $T_4$ , serum  $T_3$ ,  $FT_4$  index, serum TSH and TSH response to TRH. Moreover, determination of thyroid autoantibodies and  $^{99m}Tc$  scintigraphy were carried out. In the uninodular goitre group removal of a single hypofunctioning adenoma caused a slight but significant increase in thyrotrophic function without significant changes in serum levels of thyroid hormones. The thyrotrophic function showed a more pronounced rise in the multinodular than in the uninodular goitre group. Nonetheless a decrease in serum levels of thyroid hormones took place. Numerically, the fall was modest, albeit significant. Overt hypothyroidism developed in only one patient. According to the present knowledge of development and maintenance of goitre, our results do not indicate that thyroid replacement therapy is required as a routine measure after nodular goitre resection. Overt thyroid failure or abnormally high TSH levels—conditions in which thyroid substitution should be offered—developed only in the group operated upon for multinodular goitre.

**Key words:** non-toxic goitre, surgical treatment, pituitary thyroid axis, thyroid function.

Acta Med Scand 206 15-19 1979

Increased thyrotrophic function as the only biochemical abnormality has been described in a high percentage of patients treated surgically for non-toxic goitre (6, 9, 11, 14). Whether the finding reflects a state of subclinical hypothyroidism (5, 22) indicative of thyroid substitution therapy as a routine measure (6, 9, 14) is still a matter of debate. The

present study deals with this problem, as we have assessed the pituitary thyroid function at regular intervals in patients undergoing surgical treatment for non-toxic goitre.

### PATIENTS AND METHODS

During a one year period a consecutive series of 50 patients with benign non-toxic nodular goitre underwent goitre resection. All patients were otherwise healthy, admittedly euthyroid—clinically as well as biochemically—and received no hormonal medication. The pituitary thyroid function and clinical status were assessed before operation and 3, 6 and 12 months postsurgically.

#### Laboratory investigation

The pituitary thyroid function was determined by measuring serum total thyroxine ( $T_4$ ), serum total triiodothyronine ( $T_3$ ), serum thyroid stimulating hormone (TSH), serum TSH response to thyrotrophin releasing hormone (TRH) and  $T_3$ -resin uptake. Free  $T_4$  index ( $FT_4I$ ) was calculated by the formula: serum  $T_4 \times T_3$ -resin uptake  $\times 10^{-4}$ . Autoantibodies including thyroid microsomal and colloid (CA 2) antibodies were measured by indirect immunofluorescent technique. Thyroglobulin antibodies (CA 1) were estimated by the tanned red cell agglutination test (Laboratory of Immunology, Statens Serum Institut, Copenhagen). Moreover a  $^{99m}Tc$  pertechnetate scintigraphy of the thyroid gland was carried out using a gammacamera (Nuclear Chicago Pho/gamma HP 2) provided with a parallel hole and a pinhole collimator.

Serum  $T_4$  was measured by competitive protein binding technique (Tetrasorb, Abbott), median 100, range 58–174 nmol/l, and serum  $T_3$  by a radioimmunoassay (Abbott), median 2.4, range 1.5–3.6 nmol/l.  $T_3$ -resin uptake (Trosorb, Abbott) values were expressed proportional in relative terms to a reference serum fixed at 100, median 98, range 67–129.  $FT_4I$  showed a median value of 99, range 59–169. Serum TSH was measured by a radioimmunoassay using the kit from Pharmacia Diagnostics. The detection limit for TSH was 1.5 mU/l. Normal values ranged from  $\leq 1.5$ –6.0, median 2.0 mU/l.

**Abbreviations:**  $T_4$ =thyroxine,  $T_3$ =triiodothyronine, TSH=thyroid stimulating hormone, TRH=thyrotrophin releasing hormone,  $FT_4I$ =free  $T_4$  index.

Concerning the TRH test 200 µg of synthetic TRH (Hoechst) was rapidly injected intravenously between 9 a.m. and 11 a.m. Blood was sampled prior to (-5 and 0) and 20, 30, 40 and 60 min postinjection for determination of TSH.  $\Delta$  max TSH was defined as the difference between serum baseline TSH and serum peak TSH during the test. In females peak TSH ranged from 5.4 to 20.0 median 10.1 mU/l and  $\Delta$  max TSH from 3.9 to 17.0 median 7.5 mU/l. In males peak TSH ranged from 4.7 to 8.2 median 6.8 mU/l and  $\Delta$  max TSH from 2.6 to 5.9 median 4.3 mU/l.

The reference values defined as median and range refer to results from 103 healthy individuals aged 21-70 years examined in our laboratory. Ranges are indicated by the lowest and highest value measured.

### Statistics

Statistical analysis was performed using the Friedman test for paired data against time and the Mann-Whitney test to compare results between groups.  $P < 0.5$  was considered significant.

### Goitre specifications

In 18 patients (14 females, 4 males, age range 23-65, median 33 years) a solitary adenoma was removed. In 32 patients (28 females, 4 males, age range 25-70, median 51 years) a multinodular goitre was resected bilaterally.

In uninodular goitres the presence of a solitary adenoma was confirmed by surgery. All nodules were hypofunctioning defined by decreased uptake of  $^{99m}\text{Tc}$ . A circumscribed defect was visualized on the scintigram corresponding to the palpable mass on the neck.

In multinodular goitres the multinodularity was confirmed surgically. On the scintigram  $^{99m}\text{Tc}$  uptake was irregular with scattered non-functioning areas corresponding to the goitrous regions.

was indicated by persistence of obstructive signs, suspicion of malignancy or cosmetic reasons. From the series were patients with goitres suggesting malignancy on histological examination and patients with uninodular goitres representing a hyperfunctioning autonomous adenoma. The latter condition was suspected on the initial scintigram by demonstration of a hot nodule with partial or complete suppression of extranodular tissue and verified by  $\text{T}_3$  suppression test (100 µg of  $\text{T}_3$  daily for 7 days) followed by a TSH stimulation test (10 IU TSH intramuscularly) and repeated scans.

The median duration of goitre was significantly longer in the multinodular (8 years) than in the uninodular group (1 year). The median weight of the removed thyroid specimens was also significantly higher in the multinodular group (55 g, range 10-360) than in the uninodular group (15 g, range 5-165). Lymphoid thyroiditis was not found in any specimen. In 7 patients slightly elevated thyroid antibodies were demonstrated: the microsomal type in 6 and CA 2 type in one.

In uninodular goitres the remnant tissue was normal on gross examination whereas it showed varying degrees of nodularity in most instances in multinodular goitres. In multinodular goitre it was intended to spare a thyroid remnant of near normal gland size but in some cases a subtotal resection was done.

## RESULTS

### Pituitary thyroid function before operation

The preoperative values of serum  $\text{T}_4$ ,  $\text{FT}_4\text{I}$  and serum  $\text{T}_3$  were significantly higher in the multinodular than in the uninodular group. In both groups however values were within normal limits. No significant difference in binding properties was found between the groups. Serum basal TSH level and serum peak TSH values during TRH test in patients with multinodular goitre did not differ significantly from those in patients with uninodular goitre whereas  $\Delta$  max TSH values were significantly lower in the multinodular group (Table I).

In uninodular goitre the TSH response ( $\Delta$  max TSH) to TRH was impaired in 5 (28%) increased in one and low normal in 12 patients. In multinodular goitre the TSH response was blunted or decreased in 23 (72%) increased in one and normal in 8 patients.

### Pituitary thyroid function after operation

In the uninodular goitre group serum  $\text{T}_4$ ,  $\text{FT}_4\text{I}$  and serum  $\text{T}_3$  determined 3, 6 and 12 months after surgery did not differ significantly from preoperative levels.  $\text{T}_3$  resin uptake was unchanged. Basal TSH values were significantly raised but within normal range. The TSH response to TRH showed a modest but significant increase (Table I).

In the multinodular goitre group serum  $\text{T}_4$  and serum  $\text{T}_3$  decreased significantly. Also  $\text{FT}_4\text{I}$  lowered but not significantly.  $\text{T}_3$  resin uptake showed a significant rise indicating reduced binding capacity. Basal TSH values were significantly raised exceeding the upper normal limit in 5 patients (16%). The TSH responses to TRH showed a highly significant increase (Table I).

After operation the significant difference in thyroid hormone levels between the two groups disappeared whereas a definitely higher thyrotrophic function developed in the multinodular than in the uninodular group. Besides blunted or impaired TSH response to TRH was not found after surgical treatment. On the contrary a tendency to abnormally high responses was apparent predominantly in the multinodular group 12/32 (38%) versus 3/18 (17%).

During follow-up only one patient treated for multinodular goitre presented with clinical and biochemical evidence of hypothyroidism 34 months after operation she was placed on thyroxine.

Table 1 Effect of goitre resection on thyroid function in 18 patients with non toxic uninodular (U) and 18 patients with non toxic multinodular (M) goitre (median and range)

		Before operation	Months after operation			<i>p</i> <sup>b</sup>
			3	6	12	
serum T <sub>4</sub> (nmol/l)	U	97 78-148	101 81-127	99 80-137	105 75-134	>0.05
	M	117 61-159	98 19-137	108 62-143	107 62-133	<0.01
	<i>p</i>	<0.02	>0.05	>0.05	>0.05	
T <sub>4</sub> I (arbitrary units)	U	96 77-124	100 72-137	98 81-134	111 68-142	>0.05
	M	108 58-170	98 17-126	101 59-143	105 62-149	>0.05
	<i>p</i> <sup>a</sup>	<0.05	>0.05	>0.05	>0.05	
serum T <sub>3</sub> (nmol/l)	U	2.15 1.60-2.80	2.15 1.40-2.80	2.15 1.50-2.80	2.10 1.45-3.00	>0.05
	M	2.45 1.65-3.50	2.35 0.95-3.00	2.25 1.75-3.00	2.20 1.55-2.70	<0.01
	<i>p</i> <sup>a</sup>	<0.02	>0.05	>0.05	>0.05	
serum TSH (mU/l)	U	≤1.5 ≤1.5-3.6	2.1 ≤1.5-6.1	2.3 ≤1.5-5.4	2.3 ≤1.5-6.1	<0.01
	M	≤1.5 ≤1.5-9.5	3.6 ≤1.5-9.9	3.2 ≤1.5-9.5	3.2 ≤1.5-11.0	<0.001
	<i>p</i>	>0.05	<0.01	<0.05	<0.02	
serum peak TSH (mU/l)	U	5.4 1.8-39	7.6 2.1-49	9.0 4.0-56	8.6 3.5-60	<0.01
	M	3.9 ≤1.5-49	17.5 5.2-55	15.2 2.8-76	15.7 4.3-45	<0.001
	<i>p</i>	>0.05	<0.001	<0.01	<0.01	
Δ max TSH (mU/l)	U	3.8 0.3-36	5.3 0.6-42	6.2 2.3-51	5.8 1.7-54	<0.01
	M	2.1 0-40	14.7 3.6-47	12.9 1.3-68	13.5 2.3-41	<0.001
	<i>p</i>	<0.05	<0.01	<0.01	<0.01	

<sup>a</sup> Mann Whitney test    <sup>b</sup> Friedman test

substitution therapy and excluded from further examination. The other patients remained euthyroid both clinically and biochemically (serum T<sub>4</sub>, serum T<sub>3</sub>, FT<sub>4</sub>I). None developed recurrent goitre.

## DISCUSSION

Our study showed that 1) Removal of a single hypofunctioning thyroid adenoma leaving a remnant of normal tissue caused a slight increase in thyrotrophic function without significant change in serum levels of thyroid hormones. Although the thyrotrophic function increased significantly, basal TSH values did not rise beyond the upper normal

limit in any patient of the group. 2) In multinodular goitres, having as a rule a nodular remnant, the thyrotrophic function showed a more pronounced rise than that observed in uninodular goitres, and basal TSH values might exceed the upper normal limit. Nonetheless, a decrease in thyroid hormone levels was recorded. Numerically, the fall was slight, albeit significant, except for FT<sub>4</sub>I, and only one patient developed overt hypothyroidism.

In a recent study on surgical treatment of nodular goitre, Gernsmeier (6) found no significant change in levels of thyroid hormones or thyrotrophic function in 18 patients with remnants of normal thyroid tissue. On the other hand, the thyrotrophic function

was significantly increased in 13 patients with remnants of goitrous tissue, whereas no change was observed in thyroid hormone levels. In other studies (9-11, 14) also dealing with surgical treatment of non-toxic goitres, approximately 30% of patients developed elevated serum baseline TSH as the only biochemical abnormality. Especially subnormal levels of serum  $T_4$  were not recorded. In these studies the goitre specifications were sparse and the results were collected unsystematically. Apparently a rise in thyrotrophic function is a general feature after goitre resection, especially in the group with remnants consisting of goitrous tissue, whereas development of overt hypothyroidism is a rare occurrence.

It is well documented that the TSH response to TRH in non-toxic goitres shows a heterogeneous pattern with a definite trend towards lack of response parallel with increasing nodularity of the thyroid gland (1, 3, 4, 8, 12, 15, 16, 19). The fact that TSH responsiveness to TRH recovers after goitre resection without biochemical evidence of hypothyroidism lends support to the theory of increasing functional autonomy as a general trend in goitre evolution (2, 8). In our study the TSH response pattern to TRH before and after surgery is in complete agreement with this point of view. The fall in thyroid hormone levels after multinodular goitre resection to levels of the same order as those found in multinodular goitre group is also in accordance with the view of increased autonomy associated with the development of multinodular goitres.

The rise in thyrotrophic function after goitre resection in otherwise euthyroid patients may be explained by factors related to reduction in the mass of functioning thyroid tissue, as recently suggested by Tunbridge et al. (21) and Wilkin et al. (22) rather than by overt hypothyroidism requiring replacement therapy. This point of view is supported in our investigation by the fact that no progressive deterioration in thyroid parameters took place, except in one patient during the period of observation, irrespective of abnormally high thyrotrophic function.

It is well recognized that goitre may recur after surgical treatment, but it seems to be a minor problem based on low recurrence rates of 0-5% (10, 13, 17, 20). Factors responsible for recurrence of goitre are not well known. However, a raised thyrotrophic function may be contributory. Pickardt et al. (18) and Gernsmeier et al. (7) found a significantly

higher incidence of elevated TSH reserve in patients with recurrent than untreated goitre. But recurrence also occurred in several instances with increased thyrotrophic function. Besides, if recurrence of goitre is solely TSH dependent, a higher rate than actually found should be expected in 10% of the considerable number of patients with post-surgically elevated TSH levels.

At present it is generally agreed that the development of non-toxic goitre is TSH-dependent, a compensation for impaired thyroid hormone production. On the other hand, factors responsible for the maintenance of goitre have not been clarified. Therefore, a rational basis for thyroid replacement therapy after goitre resection still remains to be defined. However, from a theoretical point of view, conditions of overt hypothyroidism and/or abnormally high baseline TSH values should be treated with thyroid substitution.

Accordingly, our results do not indicate that thyroid replacement therapy is required routinely following goitre resection. Overt hypothyroidism, abnormally high TSH levels—conditions in which thyroid substitution should be offered—developed only in the group operated upon for multinodular goitres.

## ACKNOWLEDGEMENT

This study was supported by the Danish Research Council.

## REFERENCES

1. Blichert Toft M, Christensen C, Axelsson C & Egedorf J. TSH response pattern to TRH test: optimum time of blood sampling in sporadic euthyroid goitre. *Acta Med Scand* 204: 365, 1978.
2. Blichert Toft M, Christensen C, Axelsson C, Egedorf J, Ibsen H & Ibsen J. Effect of selective goitre resection on absent thyrotrophin response, thyrotrophin releasing hormone in idiopathic thyroid goitres. *Clin Endocrinol* 8: 95, 1978.
3. Dige Petersen H & Hummer L. Serum thyrotrophin concentrations under basal conditions and after stimulation with thyrotrophin releasing hormone in idiopathic non-toxic goiter. *J Clin Endocrinol Metab* 44: 1115, 1977.
4. Emrich D & Bahre M. Autonomy in euthyroid goitre: Maladaptation to iodine deficiency. *Clin Endocrinol* 8: 257, 1978.
5. Evered D C, Ormston B J, Smith P A, Hall J & Bird T. Grades of hypothyroidism. *Br Med J* 1: 657, 1973.
6. Gernsmeier E. Untersuchungen der Schilddrüsenfunktion mittels TRH Tests bei blauem Struma vor und nach Strumektomie. *Schweiz Wochenschr* 106: 1084, 1976.

- Gemsenjager E, Staub J J, Girard J & Hertz P. Die hypophysäre TSH Reserve in einem chirurgischen Krankengut von blander Struma und Rezidivstruma. *Schweiz Med Wochenschr* 106: 854, 1976
- Preclinical hyperthyroidism in multinodular goiter. *J Clin Endocrinol Metab* 43: 810, 1976
- Griffiths N J, Murley R S, Guhn R, Simpson R D, Woods T F & Burnett D. Thyroid function following partial thyroidectomy. *Br J Surg* 61: 626, 1974
- Heimann P. Atoxic and toxic goiter. *Acta Chir Scand (Suppl)* 289, 1962
- Hennemann G, Welsum M V, Bernard B, Docter R & Visser T J. Serum thyrotrophin concentration: an unreliable test for detection of early hyperthyroidism after thyroidectomy. *Br Med J* 4: 129, 1975
- Kirkegaard C, Faber J, Friis T, Laursen U B, Rogowski P & Siersbæk Nielsen K. Intravenous and peroral TRH stimulation in sporadic atoxic goitre. *Acta Endocrinol (Kbh)* 85: 508, 1977
- Larsen J A, Meibom J, Ramsing E M & Tjernlund A. Erfaringer fra 5-års centraliseret struma kirurgi. *Ugeskr Læger* 136: 2513, 1974
- Lenzhofer R V, Waldhausl W, Laezkovic A & Wolner E. Schilddrüsenfunktion nach Strumektomie gemessen an der TRH induzierten Ausschüttung von Thyrotropin. *Wien Klin Wochenschr* 89: 85, 1977
- Müller J M & Block M A. Functional autonomy in multinodular goiter. *JAMA* 214: 535, 1970
- Morgans M E, Thompson B D & Whitehouse S A. Sporadic non toxic goitre: an investigation of the hypothalamic pituitary thyroid axis. *Clin Endocrinol* 8: 101, 1978
- Murley R S & Ragg B M. Postoperative thyroid function and complications in relation to a measured thyroid remnant. *Br J Surg* 55: 757, 1968
- Pickardt C R, Erhardt F, Horn K, Lehnert P & Scriba P C. Therapeutische Suppression der TSH Sekretion bei blander Struma rezidiv Struma und zur rezidiv Prophylaxe nach Strumaresektion. *Verh Dtsch Ges Inn Med* 80: 1352, 1974
- Smeulders J, Docter R, Visser T J & Hennemann G. Response to thyrotrophin releasing hormone and triiodothyronine suppressibility in euthyroid multinodular goitre. *Clin Endocrinol* 7: 389, 1977
- Solem J H, Tøllås P & Wisløff F. En etter undersøkelse av pasienter operert for non toksisk struma og thyreotoksikose. *Tidsskr Nor Lægerforen* 93: 1223, 1973
- Tunbridge W M G, Harsoolis P & Goolden A W G. Thyroid function in patients treated with radioactive iodine for thyrotoxicosis. *Br Med J* 3: 89, 1974
- Wilkin T J, Storey B E, Isles T E, Crooks J & Beck J S. High TSH concentrations in euthyroidism: explanation based on control loop theory. *Br Med J* 1: 993, 1977

# The very journals for you!

---

## **Acta Chirurgica Scandinavica**

Editor L. Thoren

8 issues per volume. Free supplements. Including free subscriptions to the *Scandinavian Journal of Plastic and Reconstructive Surgery* (without suppl.) the *Scandinavian Journal of Thoracic and Cardiovascular Surgery* (without suppl.) and the *Scandinavian Journal of Urology and Nephrology* (without suppl.) Together 17 issues per year

Current volume 145/1979

Sw kr 420 per year incl postage

## **Acta Dermato-Venereologica**

Editor Nils Thyresson

6 issues per volume. Free supplements

Current volume 59/1979

Sw kr 190 per year incl postage

## **Acta Medica Scandinavica**

Editor J. Waldenström

6 issues per volume. Free supplements.

Current volumes 205-206/1979

Sw kr 375 per year (two volumes) incl postage

## **Acta Oto-Laryngologica**

Editor C. A. Hamberger

6 issues per volume. Free supplements

Current volumes 87-88/1979

Sw kr 300 per year (two volumes) incl postage

## **Pædiatrica Scandinavica**

Editor R. Zetterström

6 issues per volume. Free supplements

Current volume 63/1979

Sw kr 300 per year incl postage

## **Scandinavian Audiology**

Editor Stig Arlinger

4 issues per volume. Free supplements

Current volume 8/1979

Sw kr 175 per year incl postage

## **Scandinavian Journal of Infectious Diseases**

Editors Justus Ström and Sten Winblad

4 issues per volume. Free supplements

Current volume 11/1979

Sw kr 175 per year incl postage

## **Scandinavian Journal of Plastic and Reconstructive Surgery**

Editor Bengt Johanson

3 issues per volume. Free supplements

Current volume 13/1979

Sw kr 185 per year, incl postage

## **Scandinavian Journal of Psychology**

Editor Lars Kebabian

4 issues per volume

Current volume 20/1979

Sw kr 170 per year incl postage

## **Scandinavian Journal of Rehabilitation Medicine**

Editor Olle Håk

4 issues per volume. Free supplements

Current volume 11/1979

Sw kr 150 per year incl postage

## **Scandinavian Journal of Rheumatology**

Editor Venko Laine

4 issues per volume. Free supplements

Current volume 8/1979

Sw kr 150 per year incl postage

## **Scandinavian Journal of Social Medicine**

Editor Ragnar Berilénstam

3 issues per volume. Free supplements

Current volume 8/1979

Sw kr 140 per year incl postage

## **Scandinavian Journal of Thoracic and Cardiovascular Surgery**

Editor Viking Olov Björk

3 issues per volume. Free supplements

Current volume 13/1979

Sw kr 185 per year incl postage

## **Scandinavian Journal of Urology and Nephrology**

Editor Åke Fritjofsson

3 issues per volume. Free supplements

Current volume 13/1979

Sw kr 185 per year incl postage

## **Uppsala Journal of Medical Sciences**

Editor Gunnar Ågren

3 issues per volume. Free supplements

Current volume 84/1979

Sw kr 100 per year incl postage

---

Swedish subscribers Add V A T to all prices

Free inspection copies on request—write to

**The Almqvist & Wiksell Periodical Company**  
Box 62, S-101 20 Stockholm, Sweden

# Non-Selective and Selective $\beta$ -1-Adrenoceptor Blocking Agents in the Treatment of Hyperthyroidism

Ove R Nilsson Bengt E Karlberg Bertil Kågedal  
Lennart Tegler and Sven Almqvist

*From the Departments of Internal Medicine and Clinical Chemistry  
University Hospital Linköping Sweden*

**ABSTRACT** Treatment for one month with propranolol or atenolol, a selective  $\beta$ -1 adrenoceptor blocking agent, was evaluated in 20 hyperthyroid patients. The patients improved to the same extent on either drug, as shown by a clinical diagnostic index. Basal metabolic rate decreased by 11% during both treatments while it was unchanged in seven untreated hyperthyroid controls. Thyroxine concentration did not change during any treatment. During propranolol treatment T3 decreased from 4.6 to 3.9 nmol/l while no changes were observed during atenolol treatment or in the control group. No significant changes were seen in free T4, free T3 or rT3 concentrations on any treatment, although free T3 was observed to decrease slightly during propranolol treatment. Thus, the improvement of the clinical symptoms of hyperthyroidism cannot be explained by diminished thyroid hormone concentrations in serum, since the reduction was small during propranolol and absent during atenolol treatment.

**Keywords** thyroid hormones treatment  $\beta$  adrenergic blocking agents hyperthyroidism

Acta Med Scand 206 21 1979

Several studies have indicated that  $\beta$  adrenoceptor blocking drugs relieve many of the symptoms of hyperthyroidism (12, 19, 21, 23, 26). The secretion of thyroxine (T4) from the thyroid (28) and the radioiodine uptake in the thyroid were unchanged (10). In recent studies a decrease in serum 3,3',5'-triiodothyronine (T3) concentration was observed during propranolol treatment (11, 15, 31). Furthermore an increase in the serum concentration of 3,5'-triiodothyronine (reverse T3, rT3) simultaneously with the decrease in the serum T3 concentration was reported in patients with hyperthyroidism during short term treatment with propranolol (27). Accordingly it has been proposed that  $\beta$  blocking drugs influence the metabolism of T4 gener-

ating more biologically inactive rT3 than active T3 (27).

In earlier studies on selective  $\beta$  1 adrenoceptor blocking drugs, practolol was used in the treatment of hyperthyroidism (18, 19, 26). This drug possesses some intrinsic sympathomimetic activity which was suggested as an explanation of why practolol was inferior to propranolol in the treatment of hyperthyroidism (18, 26). In the present study we evaluated the effects of atenolol, a selective  $\beta$  1 adrenoceptor blocking agent without intrinsic sympathomimetic activity, and compared them with the effects of propranolol on the symptoms and signs of hyperthyroidism. Furthermore we investigated the effect of the drugs on the concentrations of total and free thyroid hormones in serum.

## PATIENTS AND METHODS

Twenty patients, 16 females and 4 males, aged 18-64 years (mean 45), with clinically moderate hyperthyroidism participated in the study. None of them had been previously treated for thyroid disease. Fourteen patients had a toxic diffuse goiter and six a toxic nodular goiter. Patients initially evaluated after admission to hospital for seven days, during which all clinical and biochemical investigations were performed.

All patients were examined by one of the authors (O.N.) and evaluated clinically according to a clinical diagnostic index (CDI) (6). Basal metabolic rate (BMR) and electrocardiogram (ECG) were recorded in the morning under standardized conditions. Oxygen consumption over a 10-minute period was determined twice during each investigation. A thyrotropin releasing hormone (TRH) stimulation test (200  $\mu$ g TRH i.v.) was performed in each patient.

**Abbreviations** T4=thyroxine T3=3,3',5'-triiodothyronine rT3=reverse T3 (3,3',5'-triiodothyronine) CDI=clinical diagnostic index BMR=basal metabolic rate TRH=thyrotropin releasing hormone TSH=thyrotrophin ECG=electrocardiogram



Table I Effects of propranolol or atenolol treatment on CDI and heart rate

	Before treat ment	After treatment	
		3 d	1 mo
<b>CDI</b>			
Propranolol ( <i>n</i> = 10)	22±1	—	11±2***
Atenolol ( <i>n</i> = 10)	25±2	—	14±2***
Controls ( <i>n</i> = 8)	20±2	—	21±3*
<b>Heart rate (beats/min)</b>			
Propranolol ( <i>n</i> = 10)	92±3	72±3***	73±4***
Atenolol ( <i>n</i> = 10)	96±4	71±3***	75±5***
Controls ( <i>n</i> = 8)	92±4	—	91±4*

Reexamined after 1-4 weeks

\*\*\*p&lt;0.001 compared to pretreatment

(13) Blood samples were also drawn for radioimmunoassays of serum thyrotrophin (TSH) (20) T<sub>4</sub> (17) T<sub>3</sub> (17) rT<sub>3</sub> (kit from Biodata) and free T<sub>4</sub> and T<sub>3</sub> after dialysis (7). Our normal ranges are TSH <7 mU/l T<sub>4</sub> 65-140 nmol/l T<sub>3</sub> 1.4-2.5 nmol/l rT<sub>3</sub> 0.14-0.54 nmol/l free T<sub>4</sub> 6.6-18.8 pmol/l and free T<sub>3</sub> 3.0-7.9 pmol/l. Each hormone was assayed in duplicate and in the same series in each patient.

After the initial investigations the patients were randomized into two groups for treatment. Ten patients, seven with diffuse and three with nodular goiters, were treated with 40 mg of propranolol every 6 h. The other ten with the same distribution of goiters received 50 mg atenolol every 6 h. The doses chosen are considered to be potent in terms of the effect on isoprenaline induced cardiac (2).

After three days of treatment a second BMR and ECG were recorded. Thereafter patients were discharged for outpatient treatment for three weeks and then readmitted to the ward for two days, whereupon all the initial investigations were repeated at the same time of the day.

Eight untreated hyperthyroid patients (aged 44 years, range 18-64) served as controls. On two separate occasions they underwent an evaluation which included the CDI, a TRH stimulation test and the analysis of thyroid hormones. In seven hospitalized hyperthyroid patients

without any treatment BMR was recorded on two separate days within one week to examine spontaneous variations in the course of hyperthyroidism. Only minor changes were found.

After the study 11 patients underwent subtotal thyroidectomy and three were treated with radioactive iodine. Long term treatment with carbimazole and thyroxine was given to three patients and three continued on long term treatment with  $\beta$  blocking agents.

Statistical analysis was performed by Student's *t* test. Values are given as mean  $\pm$  standard error of the mean (S.E.M.).

## RESULTS

Treatment with either propranolol or atenolol resulted in a similar improvement of the clinical symptoms and signs as indicated by the CDI and decrease in heart rate (Table I). The tolerance to both agents was good and therapy was not discontinued from any of the patients.

Treatment for three days reduced BMR in the propranolol and the atenolol group by (*p*<0.01) (Table II). The BMR was examined a third time after one month of treatment in 16 patients (9 propranolol and 7 atenolol treated). In these patients there was no significant difference between the BMR obtained after three days of treatment (250 $\pm$ 11 ml/min) and after one month of treatment (250 $\pm$ 13 ml/min).

The serum TSH concentrations were low and did not increase after TRH stimulation either before or during treatment. The thyroid hormone concentrations in serum (total T<sub>4</sub>, T<sub>3</sub> and rT<sub>3</sub> and free T<sub>4</sub> and T<sub>3</sub>) before and during treatment are shown in Table III. The serum T<sub>4</sub> concentration did not change in any group. Treatment with propranolol decreased the T<sub>3</sub> concentration from 4.6 to 3.9 nmol/l (*p*<0.05). In the atenolol group there was no change in the T<sub>3</sub> concentration. Free T<sub>4</sub> and free T<sub>3</sub> are

Table II Effects of propranolol or atenolol treatment on BMR (ml/min)

Normal values are calculated with consideration to age, sex, height and weight according to standard tables

	Calculated normal value	Before treatment	After treatment	
			3 d	1 mo
Propranolol (n=10)	189±7	273±12	244±8**	239±8**
Atenolol (n=10)	202±7	293±20	261±16**	266±26***
Controls (n=7)	182±5	243±15	239±12	—

\**p*<0.05 \*\**p*<0.01 compared to pretreatment values

\* n=9 \* n=7

Table III Serum concentrations of thyroid hormones before and after one month's treatment with propranolol (n 10) or atenolol (10) and untreated placebo controls (18)

	Propranolol		Atenolol		Untreated hyperthyroid controls	
	Before treatment	After 1 mo treatment	Before treatment	After 1 mo treatment	First visit	After 1-4 weeks
4 (nmol/l)	213+11	219+17	215+17	201+17	230+14	218+18
3 (nmol/l)	4.6+0.3	3.9+0.5*	5.0+0.4	4.8+0.5	4.6+0.7	4.3+0.4
T3 (nmol/l)	1.01+0.10	1.15+0.15	1.11+0.09	1.10+0.17	1.17+0.13	1.14+0.12
free T4 (pmol/l)	55+6	57+9	51+4	53+6	55+7	55+8
free T3 (pmol/l)	30+3	26+4	31+3	29+5	32+6	27+5

$p < 0.05$  compared to placebo treatment

concentrations did not change during treatment with either of the  $\beta$  blocking drugs

## DISCUSSION

Treatment with the  $\beta$  blocking agents in patients with hyperthyroidism caused a similar reduction in the hyperthyroid index and heart rate demonstrating favourable clinical effects of both agents. The effect on heart rate was prompt and could be noticed after the first dose. Treatment for one month did not further lower the heart rate compared to the effect on the third day.

It has been shown earlier that non-selective  $\beta$  blocking agents are effective in reducing tremor in hyperthyroidism (9, 16, 18, 19, 23) but findings with the selective  $\beta_1$  blocking agent practolol have been less certain (18). We found that the tremor disappeared in three patients treated with atenolol and in four treated with propranolol. In our opinion atenolol was as effective against tremor as propranolol.

The beneficial effect of propranolol in the treatment of hyperthyroidism is well documented (21, 23, 26). However, no study has been published where the selective  $\beta_1$  adrenoceptor blocking agent atenolol has been used with equal efficacy. Many of the clinical symptoms and signs of hyperthyroidism resemble those seen during  $\beta$  adrenergic stimulation in normal man. Atenolol lacks intrinsic sympathomimetic activity and this is probably an advantage in the treatment of hyperthyroidism compared with other  $\beta$  blocking agents.

The increased oxygen consumption in hyperthyroidism has been shown to be unchanged during treatment with  $\beta$  blocking agents (8, 12, 32) or to decrease (22). During treatment with both  $\alpha$  and

$\beta$  blocking agents a slight decrease in oxygen consumption has been found (24). Zwillch et al. (32) proposed that the metabolic abnormalities seen in hyperthyroidism are not mediated  $\beta$  adrenergically since they found no alterations during propranolol treatment but a normalization was seen when eut thyro d sm was achieved after treatment with radio active iodine. Recently Saunders et al. (27) reported a decrease in oxygen consumption in hyperthyroid patients during propranolol treatment in the same dose as we have used. They also observed a decrease in the serum T3 concentration by about 16% and proposed that the decrease in oxygen consumption might possibly be explained by reduced thyroid hormone concentrations at tissue level. We found a significant reduction of oxygen consumption during treatment for three days with propranolol as well as with atenolol. This reduction persisted during one month of treatment. The discrepancy between unchanged total and free T3 concentrations in serum and the decrease in oxygen consumption during atenolol treatment do not support the suggestion that the fall in oxygen consumption is caused by a diminished serum T3 concentration. Another reason for the decrease in oxygen consumption during  $\beta$  blockade may be the reduction of the heart rate which was similar in both treatment groups.

We found a small decrease in serum T3 concentration during propranolol treatment but no change was seen in the atenolol group. There was a tendency for the free T3 concentration to decrease during propranolol treatment but this change was not significant ( $p < 0.1$ ). Earlier studies have shown a fall in serum T3 concentrations during treatment with 80-160 mg propranolol daily (11, 25, 31). Using

higher doses of propranolol (320 mg daily) Verhoeven et al (27) obtained a decrease in serum T3 in their patients although T3 still remained above the normal reference interval. We used a moderate dose of each drug, which gave clinical improvement but caused no reduction of T3 concentration during atenolol treatment and only a small reduction during propranolol treatment. Variations in the course of hyperthyroidism in different patients may explain divergent results during treatment with  $\beta$ -blocking agents. In our hyperthyroid controls we registered small spontaneous variations in serum T3 concentrations.

In a comparative study on the effects of propranolol and practolol in the management of hyperthyroidism Murchinson et al (18) noticed a decrease in serum T3 during propranolol but no changes during practolol treatment. We used another selective  $\beta$ -1 adrenoceptor blocking agent, atenolol which did not influence the T3 concentration during treatment. It may be that the effects of propranolol on the metabolism of thyroid hormones involve  $\beta$ -2 adrenergic mechanisms.

The peripheral conversion of T4 to T3 is decreased in various non-thyroidal diseases (3, 4, 30) and during treatment with dexamethasone (5, 29) and propylthiouracil (1, 14). Compared to other conditions acting on the conversion of T4 to T3 and respectively the influence on the conversion of these drugs in hyperthyroidism seems to be less in degree and importance. The effect of these drugs seems to be mediated by a blockade at the cellular receptor level rather than an influence on the metabolism of thyroid hormones.

## REFERENCES

- 1 Aboud J & Larsen P R. Triiodothyronine and thyroxine in hyperthyroidism. Comparison of the acute changes during therapy with antithyroid agents. *J Clin Invest* 54: 201, 1974.
- 2 Barrett, A. M. The pharmacology of atenolol. *Post grad Med J (Suppl)* 3: 48, 1977.
- 3 Burger A, Nicod P, Suter P & Valletton M. B. Reduced active thyroid hormone levels in acute illness. *Lancet* i: 653, 1976.
- 4 Chopra, I J, Chopra U, Smith S R, Reza, M. & Solomon D H. Reciprocal changes in serum concentration of 3,3',5'-triiodothyronine (reverse T3) and 3,3',5'-triiodothyronine (T3) in systemic illness. *J Clin Endocrinol Metab* 41: 1043, 1975.
- 5 Chopra, I J, Williams D E, Orgiazzi J J & Solomon D H. Opposite effects of on serum concentrations of 3,3',5'-triiodothyronine (reverse T3) and 3,3',5'-triiodothyronine (T3). *J Endocrinol Metab* 41: 911, 1975.
- 6 Crooks J, Murray J P C & Wayne E J. Statistical methods applied to the clinical diagnosis of thyrotoxicosis. *Q J Med* 28: 211, 1959.
- 7 Ekins R P & Ellis S M. The radioimmunoassay of free thyroid hormones in serum. In: *Thyroid research* (ed J Robbins and L. E. Braverman) p. 49. *Certa Medica*, Amsterdam, 1976.
- 8 Georges L. P, Santangelo R P, Mackin J, Canary J J. Metabolic effects of propranolol in thyrotoxicosis. I. Nitrogen, calcium and hydroxyproline. *Metabolism* 24: 11, 1975.
- 9 Grossman W, Robin N I, Johnson L W, Br H, Selenkow H A & Dexter L. Effects of blockade on the peripheral manifestations of thyrotoxicosis. *Ann Intern Med* 74: 875, 1971.
- 10 Hadden D R, Bell T K, McDevitt D G, St R, G, Montgomery D A D & Weaver J A. Propranolol and the utilization of radioiodine by the human thyroid gland. *Acta Endocrinol* 61: 393, 1971.
- 11 Harrower A D B, Fyffe J A, Horn D, Strong, J A. Thyroxine and triiodothyronine in hyperthyroid patients during treatment with propranolol. *Clin Endocrinol* 7: 41, 1977.
- 12 Howitt, G & Rowlands D J.  $\beta$ -sympathetic blockade in hyperthyroidism. *Lancet* i: 628, 1966.
- 13 Karlberg B & Almqvist S. Effects of increased doses of pyroglutamyl histidylprolinamide on thyrotrophin levels in normal subjects. *Acta Endocrinol* 70: 196, 1972.
- 14 Laurberg P & Weeke J. Opposite variations in serum T3 and reverse T3 during propylthiouracil treatment of thyrotoxicosis. *Acta Endocrinol* 87: 88, 1975.
- 15 Lott G, Delitala G, Devilla L, Alagna S, & Sala, A. Reduction of plasma triiodothyronine induced by propranolol. *Clin Endocrinol* 6: 405, 1977.
- 16 Marsden C D, Gimlette T M D, McAllist G, Owen, D A L & Miller T N. Effect of adrenergic blockade on finger tremor and a reflex time in anxious and thyrotoxic patients. *Endocrinol* 57: 353, 1968.
- 17 Mituma, T, Colucci J, Shenkman L & Fisher C. S. Rapid simultaneous radioimmunoassay of triiodothyronine and thyroxine in unextracted plasma. *Biochem Biophys Res Commun* 46: 2107, 1972.
- 18 Murchinson L E, Bewsher P D, Chesters & Ferner W R. Comparison of propranolol and practolol in the management of hyperthyroidism. *Clin Pharmacol* 3: 273, 1976.
- 19 Nelson J K L & McDevitt D G. Comparison of propranolol and practolol in hyperthyroidism. *Br J Clin Pharmacol* 2: 411, 1975.
- 20 Odell W D, Wilber J F & Unger R D. Study of thyrotrophin physiology by means of radioimmunoassay. *Recent Prog Horm Res* 23: 47, 1967.
- 21 Ramsay I. Adrenergic  $\beta$ -receptor blockade in hyperthyroidism. *Br J Pharmacol* 2: 385, 1975.
- 22 Saunders J, Hall S E H, Crowther A. & Son P H. The effect of propranolol on thyroid hormone

- 2 and oxygen consumption in thyrotoxicosis. *Clín Endocrinol* 9: 67, 1978
- 3 Shanks R G, Lowe D C, Hadden D R, McDevitt D G & Montgomery D A D. Controlled trial of propranolol in thyrotoxicosis. *Lancet* i: 993, 1969
- 4 Stout B D, Wener L & Cox J W. Combined alpha and beta sympathetic blockade in hyperthyroidism. *Ann Intern Med* 70: 963, 1969
- 5 Theilade P, Hansen J M, Skovsted L, Faber J, Krøgaard C, Friis T & Sørensen N. Propranolol influences serum T<sub>3</sub> and reverse T<sub>3</sub> in hyperthyroidism. *Lancet* 2: 363, 1977
- 6 Turner P.  $\beta$ -adrenergic receptor blocking drugs in hyperthyroidism. *Drugs* 7: 48, 1974
- 7 Verhoeven R P, Visser T J, Docter R, Henne-man G & Schalekamp M A D H. Plasma thyroxine, 3,3,5-triiodothyronine and 3,3,5-triiodothyronine during  $\beta$ -adrenergic blockade in hyperthyroidism. *J Clin Endocrinol Metab* 44: 1002, 1977
- 28 Wartofsky L, Dumond R C, Noel G L, Frantz A G & Earle J M. Failure of propranolol to alter thyrodioid release, thyroxine turnover, or the TSH and PRL responses to thyrotropin releasing hormone in patients with thyrotoxicosis. *J Clin Endocrinol Metab* 41: 485, 1975
- 29 Westgren U, Åhrén B, Burger A, Ingemansson S & Melander A. Effects of dexamethasone, deoxycorticosterone and ACTH on serum concentrations of thyroxine, 3,3,5-triiodothyronine and 3,3,5-triiodothyronine. *Acta Med Scand* 207: 89, 1977
- 30 Westgren U, Burger A, Levin K, Melander A, Nilsson G & Pettersson U. Divergent changes in serum 3,3,5-triiodothyronine and 3,3,5-triiodothyronine in patients with acute myocardial infarction. *Acta Med Scand* 201: 269, 1977
- 31 Wersinga W M & Touber J L. The influence of  $\beta$ -adrenoceptor blocking agents on plasma thyroxine and triiodothyronine. *J Clin Endocrinol Metab* 45: 293, 1977
- 32 Zwillich C W, Matthay M, Potts D E, Adler R, Hodeid F & Weil J V. Thyrotoxicosis: Comparison of effects of thyroid ablation and beta adrenergic blockade on metabolic rate and ventilatory control. *J Clin Endocrinol Metab* 46: 491, 1978



## Angiotensin-Converting Enzyme in Sarcoidosis

Frode K. Rømer

From Departments of Medicine C and Thoracic Medicine B  
Kommunehospitalet Århus Denmark

**ABSTRACT** Using a spectrophotometric assay with hippuryl-L-histidyl-L-leucine as substrate, angiotensin-converting enzyme (SACE) was determined in 85 sarcoidosis patients, 116 healthy controls and 150 patients with various non-sarcoid diseases. The controls showed no sex or age variation and had SACE levels of  $24.4 \pm 6.2$  U/ml (mean  $\pm$  1 S.D.), giving a normal range (mean  $\pm$  2 S.D.) of 12.0–36.8 U/ml. In contrast, the sarcoidosis patients had SACE values of  $38.4 \pm 14.4$  U/ml, with the highest values in cases with active sarcoidosis and duration of disease longer than two years ( $49.0 \pm 12.7$  U/ml). A total of 41% of the sarcoidosis patients had elevated SACE, in the chronic active group 85%. Patients with renal failure, Hodgkin's disease and other malignant lymphoma had low SACE, whereas patients with lung cancer and tuberculosis had normal SACE values. Among 266 patients with non-sarcoid diseases and healthy controls, only two had slightly elevated SACE, but so far we have not found SACE above 40 U/ml in other than sarcoidosis patients. An elevated SACE is rather specific in sarcoidosis and seems to be a useful supplement to existing diagnostic measures.

**Key words:** angiotensin-converting enzyme, sarcoidosis, Hodgkin's disease, lung cancer, renal failure.

Acta Med Scand 206: 27–30, 1979.

The diagnosis of sarcoidosis is based on clinical signs, chest X-ray (CXR) and occurrence of non-caseating epithelioid granulomas in tissue biopsy or Kveim-Siltzbach test (13). For clinical purposes, however, the clinical picture together with a characteristic CXR is often sufficient (23). A Kveim-Siltzbach test is positive in 50–90% of the cases (7) but as a high quality antigen is not generally available, other ways have been proposed to confirm the diagnosis. In this respect,  $\alpha$ -lysozyme attracted attention some years ago because it was found to be elevated in many cases of active sarcoidosis (16). But as elevated values also occur in several other disorders,  $\alpha$ -lysozyme is rather unspecific as a diagnostic test (15). Therefore Lieberman's first paper

on elevated serum angiotensin-converting enzyme (SACE) in sarcoidosis (8) aroused great interest, especially as only Gaucher's disease (11) and leishmaniasis (12) have subsequently been associated with consistently elevated SACE.

The purpose of the present study is to evaluate the diagnostic value of SACE analysis in a large group of sarcoidosis patients compared with patients with other pulmonary diseases and diseases in which symptoms and signs might be caused by sarcoidosis.

## SUBJECTS

The series consisted of 85 sarcoidosis patients, male/female ratio 46/39, mean age 37 years (range 18–70) with a mean observation time of five years (range six months–37 years). All patients were of the Caucasian race.

According to CXR at the time of blood sample, the sarcoidosis patients were staged 0–III (18). Nineteen patients had no CXR abnormalities (stage 0), 22 had mediastinal lymphadenopathy alone (stage I), 35 had mediastinal lymphadenopathy and pulmonary infiltrations (stage II) and nine patients had pulmonary changes alone (stage III).

Because CXR staging corresponds only roughly to disease activity, the patients were grouped as follows:

(a) *Active sarcoidosis*: Clinical signs of active disease including progressive or regressive changes in the CXR within the last two years. These patients could be subdivided into (aa) *subacute sarcoidosis* with a duration shorter than two years, and (ab) *chronic active sarcoidosis* with a duration of disease longer than two years.

(b) *Inactive sarcoidosis*: No signs of disease activity (or no changes in CXR) within the last two years, mainly patients in a fibrotic stage of the disease.

(c) *Remitted sarcoidosis*: Resolved cases with no signs or residue of the disease at all, clear CXR.

Furthermore, 150 sera were tested from patients with a variety of other diseases. The controls were 116 healthy volunteers and blood donors, aged 18–65 years.

## METHOD

The principle of a substrate analogue was used. From the substrate Hippuryl-histidyl-leucine (HHL), ACE liberates

**Abbreviations:** ACE=angiotensin-converting enzyme; SACE=serum ACE; CXR=chest X-ray; HHL=hippuryl-histidyl-leucine.

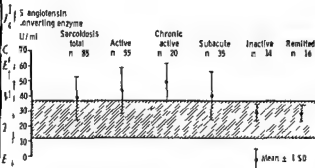


Fig. 1 Distribution of SACE in 85 sarcoidosis patients subdivided into active, inactive and remitted cases. Hatched area = normal range.

hippuric acid, which can be measured spectrophotometrically (3). The modification of Lieberman (10) was used with some minor changes. The calculations were made according to Lieberman (10) after correcting an error of calculation in his paper, which yielded results three times too low (9). Blood samples were obtained by venipuncture and serum was stored at  $-20^{\circ}\text{C}$  until analysis.

The results are expressed as U/ml ACE units being equivalent to nmoles hippuric acid formed per minute at  $37^{\circ}\text{C}$  under standard assay conditions (10). A one-hour assay was used. SACE values are expressed in this paper as mean  $\pm$  1 S.D.

The HHL was obtained during the first months from Calbiochem, Luzerne, Switzerland, but later we used HHL from Bio-Science Products, Reussbühl, Switzerland. All sera tested with both substrates gave identical SACE values.

Statistical calculations were performed by Student's *t*-test or  $\chi^2$ -test. Significance level was 5%.

## RESULTS

### Control series

Among 116 healthy controls, SACE was  $24.4 \pm 6.2$  U/ml (range 8.3–38.9). No sex or age differences

Table I SACE (mean  $\pm$  1 S.D.) in 116 healthy controls and 85 sarcoidosis patients

	N	SACE (U/ml)	p
Controls	116	$24.4 \pm 6.2$	
Sarcoidosis total	85	$38.3 \pm 14.4$	<0.001
a) Active	55	$43.4 \pm 15.3$	<0.001
aa) Subacute	35	$40.1 \pm 15.9$	<0.001
ab) Chronic	20	$49.0 \pm 12.7$	<0.001
b) Inactive	14	$29.1 \pm 5.6$	<0.01
c) Remitted	16	$28.6 \pm 5.5$	
aa + b) Chronic cases	34	$40.8 \pm 14.3$	<0.001

Difference between aa and ab:  $p < 0.025$

Difference between a and b + c:  $p < 0.001$

were noted and food time of day or previous venous stasis had no influence on SACE. The ml range of SACE was calculated as  $\pm 2$  S.D. i.e. 12.0–36.8 U/ml.

### Sarcoidosis patients

Among 85 sarcoidosis patients, SACE was  $38.4 \pm 14.4$  U/ml, which was significantly higher than among the controls ( $p < 0.001$ ). SACE in clinical subgroups of sarcoidosis is shown in Fig. 1 and Table I.

The subgroup chronic active sarcoidosis had the highest mean values, significantly higher than subacute cases. Inactive sarcoidosis and remitted cases had values within the normal range, but these groups had combined mean values higher than the controls.

Furthermore, the proportion of patients with elevated SACE differed between the subgroups of sarcoidosis (Table II). There was a trend toward a higher percentage of elevated SACE among patients compared with females (22/46 (48%) vs. 13/39 (33%) respectively), but this difference was not significant and there were no differences in mean SACE between the sexes.

No difference was noted between different groups or between patients with or without pulmonary sarcoidosis. Regarding the CXR, patients in stages 0 and III had lower values than patients in stages I and II (mean 30.7 and 41.9 respectively) ( $p < 0.005$ ).

### Other diseases

In addition, 150 sera from patients with various diseases were analyzed (Table III). SACE in patients with lung cancer and tuberculosis was within the lower normal range, but not significantly higher than in the controls. Malignant lymphomas had

Table II Incidence of elevated SACE in 85 sarcoidosis patients

	Patients with SACE > 36.8 U/ml	
	N	n
Sarcoidosis total	85	35
a) Active	55	34
aa) Subacute	35	17
ab) Chronic	20	17
b + c) Inactive and remitted	30	1

Table III SACE (mean  $\pm$  I S D) and cases with elevated SACE among healthy controls and patients with diseases other than sarcoidosis

	N	SACE (U/ml)	p	SACE >36.8 U/ml	
				n	%
Controls	116	24.4 $\pm$ 6.2		1	0.8
Lung cancer	26	22.8 $\pm$ 5.5	n.s.		
Lung tuberculosis	7	22.6 $\pm$ 5.9	n.s.		
Hodgkin's disease	23	21.3 $\pm$ 7.6	<0.02	1	4
Other malignant lymphomata	18	20.4 $\pm$ 6.8	<0.02		
Non sarcoid uveitis	20	24.1 $\pm$ 7.0	n.s.		
Renal failure	15	20.3 $\pm$ 6.9	<0.02		
Other diseases	41	25.2 $\pm$ 6.7	n.s.		
Total	266			2	0.8

n.s. not significant

significantly low SACE. But one patient with Hodgkin's disease had slightly elevated SACE 38.9 U/ml. Furthermore 15 patients with non sarcoid renal failure had low SACE. Normal SACE was found in four patients with non sarcoid hypercalcaemia due to cancer or primary hyperparathyroidism. In contrast three patients with sarcoidosis hypercalcaemia and renal failure all had elevated SACE. Normal SACE was also found in 37 patients with other diseases i.e. pneumonia various heart diseases, arterial hypertension etc.

In the total series only two non sarcoid patients out of 266 (one of the normal controls and one patient with Hodgkin's disease) had elevated SACE lower than 40 U/ml in both. So far SACE higher than 40 U/ml has been found in this series only in sarcoidosis patients.

## DISCUSSION

ACE has an important place in the renin-angiotensin system by converting angiotensin I to angiotensin II. It is located in the vascular endothelium probably in most organs but with far the highest concentrations in the lungs (22). Here it is found in small caveolae in the lung capillaries in close contact with the bloodstream (17).

Indeed it was surprising that Lieberman (8) reported high SACE in sarcoidosis because sarcoidosis had not been associated before with the renin-angiotensin system. This finding has been confirmed in other studies using the same or different techniques (1, 4, 5, 6, 14).

Whether a high SACE reflects a high production

in sarcoid tissue or a hampered decomposition is unknown. But the finding of a ten fold higher ACE concentration in sarcoid lymph nodes (20)—together with signs of secretory function of the sarcoid epithelioid cells (2)—suggests that ACE is synthesized in sarcoid lymph nodes. In contrast no increased ACE activity has been found in tuberculous granulomas (20) or in experimental Freund's granulomas (21).

There has been disagreement concerning age and sex variations for SACE in normals (1, 10) but in this series no differences were detected between males and females or between different age groups.

This series confirms that SACE is elevated in sarcoidosis also in a Scandinavian population namely in 41% of the total series. However there was a distinct difference associated with disease activity. While inactive or resolved cases had nearly normal values 62% of the patients with active sarcoidosis had high SACE levels especially in the group with a chronic course longer than two years in which 85% of the patients had elevated SACE. Only one of the normal controls and one patient with Hodgkin's disease had high SACE indicating a high specificity of SACE especially if an arbitrary upper limit of 40 U/ml is chosen. So far we have found no patients without sarcoidosis with SACE higher than that.

In other diseases which can give diagnostic difficulties with sarcoidosis (lung cancer, tuberculosis, uveitis, lymphomata, hypercalcaemia and renal failure) normal or low SACE values were found as in patients with a variety of other diseases. Significantly low values in lung cancer have been reported



10 19) Although our patients with lung cancer had a rather low SACE their mean value did not differ significantly from that of the control group.

The mean value of SACE in patients with Hodgkin's disease and other lymphomas was significantly lower than in controls. However, as mentioned above, one patient with Hodgkin's disease had an elevated SACE (but lower than 40 U/ml).

It was of special interest to note that patients with renal failure and/or non-sarcoid hypercalcaemia had low or normal SACE, since s-lysozyme is elevated both in active sarcoidosis and in renal failure (15) and therefore is of no diagnostic value in evaluating hypercalcaemic states with renal failure which occasionally may be caused by sarcoidosis. But it is necessary to draw the blood sample before initiation of prednisone treatment because corticosteroids seem to normalize a high SACE in sarcoidosis (19).

It seems that SACE should be a useful diagnostic tool for the clinician, though without replacing a careful clinical examination, CXR and in many cases histological evidence of non-caseating epithelioid granulomas. A high SACE nearly always indicates active sarcoidosis, while a normal SACE is of doubtful value in this respect. Furthermore, SACE probably may be valuable in following the course and effect of treatment (19) but in this respect one must wait for the results from long term studies.

## ACKNOWLEDGEMENT

This study has been supported by the Danish Medical Research Council (Sættens lægevidenskabelige forskningsråd).

## REFERENCES

- 1 Ashotoh, K. & Keighley, J. F. H. Diagnostic value of serum angiotensin converting enzyme activity in lung diseases. *Thorax* 31: 552, 1976.
- 2 Carr, J. & Norris, P. The fine structure of human macrophage granules in sarcoidosis. *J. Pathol.* 122: 29, 1977.
- 3 Cushman, D. W. & Cheung, H. S. Spectrophotometric assay and properties of the angiotensin-converting enzyme of rabbit lung. *Biochem. Pharmacol.* 20: 1637, 1971.
- 4 Farburg, B. L., Schoenberger, M. D., Bachus, B. & Snider, G. L. Elevated serum angiotensin I converting enzyme in sarcoidosis. *Ann. Rev. Resp. Dis.* 114: 525, 1976.
- 5 Friedland, J. & Silverstein, E. A sensitive fluorimetric assay for serum angiotensin-converting enzyme. *Am. J. Clin. Pathol.* 66: 416, 1976.
- 6 — Sensitive fluorimetric assay for serum angiotensin-converting enzyme with the natural substrate, angiotensin I. *Am. J. Clin. Pathol.* 68: 225, 1977.
- 7 Israel, H. L. Observations on the mechanism and specificity of the Kunitz-reaction. In: *Proceedings of the 11th International Conference on Sarcoidosis*, H. Iwata & Y. Hosoda (eds), pp. 60-67. University Press, Tokyo, 1974.
- 8 Lieberman, J. A new confirmatory test for sarcoidosis. *Am. Rev. Resp. Dis.* 109: 743, 1974.
- 9 — The specificity and nature of serum-angiotensin converting enzyme (serum ACE) elevations in sarcoidosis. *Ann. NY Acad. Sci.* 278: 488, 1976.
- 10 — Elevation of serum angiotensin-converting enzyme (ACE) level in sarcoidosis. *Am. J. Med. Sci.* 1975.
- 11 Lieberman, J. & Beutler, E. Elevation of angiotensin-converting enzyme in Gaucher's disease. *Engl. J. Med.* 294: 1442, 1976.
- 12 Lieberman, J. & Rea, T. H. Elevation of serum angiotensin-converting enzyme in leprosy. *Clin. Pathol.* 25: 145 A, 1977.
- 13 Mitchell, D. N. & Scadding, J. G. Sarcoidosis. *Rev. Resp. Dis.* 110: 774, 1974.
- 14 Oparil, S., Low, J. & Koerner, T. J. Altered angiotensin I conversion in pulmonary disease. *Clin. Mol. Med.* 51: 537, 1976.
- 15 Oserman, E. F., Canfield, R. E. & Beychok, S. L. *Lysozyme*. Academic Press, New York and London, 1974.
- 16 Pascual, R. S., Gee, J. B. L. & Finch, S. C. I. Accuracy of serum lysozyme measurements in diagnosis and evaluation of sarcoidosis. *N. Engl. J. Med.* 289: 1074, 1973.
- 17 Ryan, L. S. & Ryan, J. W. Correlations between fine structure of the alveolar-capillary unit and metabolic activities. In: *Metabolic functions of lung* (ed. Y. S. Bakhle & J. R. Vane), pp. 197-200. Dekker, New York and Basel, 1977.
- 18 Siltzbach, L. E. Sarcoidosis: clinical features and management. *Med. Clin. North Am.* 51: 483, 1967.
- 19 Silverstein, E., Friedland, J., Kuti, M. & Lyons, H. A. Increased serum angiotensin converting enzyme activity in sarcoidosis. *Isr. J. Med. Sci.* 13: 995, 1977.
- 20 Silverstein, E., Friedland, J., Lyons, H. A. & Gotlib, A. Markedly elevated angiotensin converting enzyme in lymph nodes containing non-necrotizing granulomas in sarcoidosis. *Proc. Natl. Acad. Sci. U.S.A.* 73: 2137, 1976.
- 21 Silverstein, E., Friedland, J. & Setton, C. Angiotensin-converting enzyme in macrophages and Freund adjuvant granuloma. *Isr. J. Med. Sci.* 14: 314, 1978.
- 22 Soffer, R. L. Angiotensin-converting enzyme and regulation of vasoactive peptides. *Ann. Rev. Biochem.* 45: 73, 1976.
- 23 Winterbauer, R. H., Belic, N. & Moores, K. D. Clinical interpretation of bilateral hilar adenopathy. *Ann. Intern. Med.* 78: 65, 1973.

# The Expression of a Human B-Lymphocyte Antigen on Cells in Different Types of Leukaemia

Ingemar Turesson Enk Berntorp and Olle Zettervall

From the Department of Internal Medicine, University of Lund  
Malmö General Hospital, Malmö, Sweden

**ABSTRACT** The expression of a B-cell antigen on the surface of leukaemic cells from patients with various forms of leukaemia was studied by direct immunofluorescence using a rabbit antiserum against chronic lymphocytic leukaemia (CLL) cells. The antigen was found on normal peripheral blood B-lymphocytes and on the majority of lymphocytes from patients with CLL. Most normal peripheral blood monocytes and blasts from patients with acute myeloblastic leukaemia, acute myelomonocytic leukaemia or acute lymphoblastic leukaemia of T-cell type did not carry the antigen but a minority of such cells were weakly stained. In two of three patients with blast transformation of chronic myelocytic leukaemia, a high proportion of the blasts carried the antigen. It was also found on the surface of the hairy cells from two cases of leukaemic reticuloendotheliosis.

These cells also carried Fc receptors and immunoglobulin with restricted heterogeneity ( $\mu$ ,  $\lambda$  and  $\alpha$ ,  $\mu$ ,  $\delta$ ,  $\kappa$ , respectively). The cellular distribution of the B-cell antigen differs to some extent from that of Ia-like antigens detected by antisera against purified B-cell membrane products. The demonstration of the antigen as well as immunoglobulin of a single light chain type on the surface of hairy cells strongly supports the B-lymphocyte origin of these cells.

**Key words:** B-cell antigen, surface membrane immunoglobulin, leukaemia, leukaemic reticuloendotheliosis.

Acta Med Scand 206: 31-36, 1979.

Lymphocytes can be identified by heterologous antisera raised against whole B-cells or B-cell membrane products. Such antisera may vary in their reactions with different cells. Most antisera raised against enzyme- or detergent-solubilized cell membrane preparations seem to detect antigens which are related to the Ia-antigens in rodents (15, 15, 22, 33, 34, 37). These antisera block the reaction of human alloantisera with B-lymphocytes as well as

the stimulation in mixed lymphocyte culture and the chemical structure of the antigen is similar to that of mouse Ia-antigens (6, 25, 33, 37). In man, Ia-like antigens have been detected not only on B-lymphocytes (normal peripheral blood B-lymphocytes, chronic lymphocytic leukaemia (CLL) lymphocytes, lymphoblastoid B-cell lines) but also on monocytes, blasts in acute lymphocytic leukaemia of non T-non B cell type, blast crisis in chronic myelocytic leukaemia (CML) and most cases of acute myeloblastic leukaemia (AML) (5, 32, 33, 34, 37, 39). They are also present on immature blast cells in normal bone marrow but not on more differentiated cells in the myeloid series (23, 36).

We have recently reported on a heterologous antiserum against CLL lymphocytes that identifies a B-cell-specific antigen not identical with Ia-antigens (4). This report concerns the distribution of this antigen on the cells in different forms of leukaemia.

## STUDY POPULATION

**Healthy individuals.** This group consisted of 10 members of the laboratory staff. Only peripheral blood mononuclear cells were examined.

**Chronic lymphocytic leukaemia.** All 11 patients had peripheral blood lymphocytosis and a diffuse lymphocytoid infiltration of the bone marrow. Only peripheral blood was examined.

**Acute leukaemia.** Five of the 11 patients in this group had AML, two acute myelomonocytic leukaemia

**Abbreviations:** CLL=chronic lymphocytic leukaemia, CML=chronic myelocytic leukaemia, AML=acute myeloblastic leukaemia, AMML=acute myelomonocytic leukaemia, ALL=acute lymphoblastic leukaemia, FITC=fluorescein-isothiocyanate, TRITC=tetramethylrhodamine-isothiocyanate, PBS=phosphate-buffered saline, BSA=bovine serum albumin, SRBC=sheep red blood cells, sig=surface membrane immunoglobulin.

(AMML) one acute lymphoblastic leukaemia (ALL) and three blastic transformation of CML. All patients had a high peripheral WBC with a dominance of blasts. Further classification was based on cell morphology, intracellular peroxidase staining and serum and urine lysozyme determinations.

**Hairy cell leukaemia.** Both of the two patients had circulating mononuclear cells with a typical hairy appearance in phase contrast microscopy and with high activity of tartrate resistant acid phosphatases. Both patients were treated by splenectomy and the diagnosis of leukaemic reticuloendotheliosis was confirmed on histological examination of the large spleens. Agarose gel electrophoresis of plasma and urine revealed no monoclonal Ig in either case.

## METHODS

**Antisera.** An anti B-cell serum (antiserum 7420) was raised in one rabbit by immunization with lymphocytes from a patient with CLL. The preparation of FITC (fluorescein isothiocyanate) labelled  $F(ab)_2$  fragments of antiserum IgG absorptions and testing for B lymphocyte specificity have been described earlier (4). FITC labelled  $F(ab)_2$  fragments of IgG from normal rabbit serum were prepared according to the same procedure.

FITC-labelled antisera against alpha mu gamma and delta heavy chains, TRITC (tetramethyl rhodamine isothiocyanate) labelled polyvalent antiserum against human Ig heavy and light chains and TRITC labelled  $F(ab)_2$  fragments of goat antihuman Fab were obtained from Nordic Immunological Laboratories, Tilburg, the Netherlands. FITC labelled antisera against kappa and lambda chains were from Dakopatts, Copenhagen, Denmark. Labelled  $F(ab)_2$  fragments of rabbit IgG against mu and lambda chains were produced at the laboratory using the method of Forsum (14). The specificity of conjugates was tested on myeloma and macroglobulin aemia bone marrow smears as described earlier (35). To stain all cells with surface membrane Ig, the TRITC labelled polyvalent whole IgG was used in the early phase of the study and the TRITC labelled  $F(ab)_2$  fragments were used later. Since no difference in sIg positive cells in healthy individuals was observed, these groups are not reported separately.

**Latex phagocytosis.** The mononuclear cells from peripheral blood were suspended in medium RPMI 1640 at a concentration of  $1 \times 10^6$  cells/ml. 0.020 ml of 0.8 µm latex particles (Bacto) were added to 10 ml of the cell suspension. After incubation for 60 min at 37°C in a water bath, the cells were washed with prewarmed PBS-BSA (phosphate buffered saline, pH 7.2 with 1% bovine serum albumin) twice before immunofluorescent staining.

**Immunofluorescence.** One drop (approximately 30 µl) of the cell suspension containing  $1.5 \times 10^6$  cells was mixed with one drop of the FITC or TRITC conjugate in plastic tubes. These were incubated at +4°C for 30 min with intermittent shaking. The cells were washed twice with PBS-BSA at +4°C and mounted in buffered glycerol, pH 7.8. The slides were examined in a Leitz Orthoplan fluorescence microscope equipped with epi illumination and

filter systems for narrow band excitation of FITC, TRITC (20). The cells were first identified in phase contrast transmitted light and then examined for fluorescence with incident light. Two hundred cells, the typical morphology of small lymphocytes, were counted and the percentage of fluorescent cells was calculated. In the CLL patients, larger lymphoid cells, sometimes more abundant and were included in the preparations from patients with acute leukaemia, leukemic reticuloendotheliosis and hairy cells, respectively. Blasts were identified by their morphology in phase contrast and the percentage of these cells with membrane fluorescence was calculated. In the cell preparations for staining of monocytes, these were identified by morphology or by intracellular accumulation of latex particles. To demonstrate intracellular peroxidase, the cells were smeared on glasses after the immunofluorescence staining, fixed with formalin and stained by the method of Karnovsky (24). No counterstain was applied, but the slides were mounted in buffered glycerol and the percentage of peroxidase positive cells with membrane fluorescence were calculated.

**Detection of receptor for Fc of IgG and for sheep erythrocytes (E rosettes).** Rhodamine conjugated heat aggregated human IgG was prepared as described previously (4). It was used for immunofluorescence staining of mononuclear cells as described above. E rosettes were prepared according to Pattengale and Reichelderfer (27). Ficoll to stabilize the rosettes.

## RESULTS

### *Peripheral blood mononuclear cells in healthy individuals*

The percentage of small lymphocytes stained with the 7420 conjugate (mean 12.5%, range 9–22%) was in close agreement with the percentage of surface membrane immunoglobulin (sIg) positive lymphocytes (mean 12.7%, range 9–23.5%). In seven individuals, when staining for sIg and cell antigen was performed simultaneously, the percentage of B cells obtained by the two methods were very similar (Fig. 1).

Peripheral blood monocytes were examined in one healthy individual using three different methods to identify the cells: morphology in phase contrast microscopy, phagocytosis of latex particles, and staining for intracellular peroxidase. The percentage of monocytes in mononuclear cell suspensions was very similar by these three criteria: 27–33%, 33% respectively. The staining reaction with the 7420 conjugate, however, varied somewhat. A weak positive reaction was obtained with a small population of monocytes identified by morphology in phase contrast microscopy or latex phagocytosis.

Table I Peripheral blood lymphocytes in healthy individuals and patients with CLL. % of cells with 7470 B-cell antigen and with sIg (stained with FITC labelled Fab<sub>1</sub> fragments of antihuman b or TRITC-labelled IgG against human Ig)

	Lymphocytes (%)	
	B-cell antigen-positive	sIg-positive
Healthy individuals		
Mean	12.5	12.7
Range	9-22	9-23.5
	10	10
CLL patients		
Mean	69	84
Range	22-100	76-99
	13	7

11% and 13% respectively) while in the majority of the monocytes there was no certain staining. The peroxidase-positive cells were all unstained with the FITC conjugate. In all preparations a subpopulation of small lymphocytes (9-12%) stained with a strong and distinct membrane fluorescence.

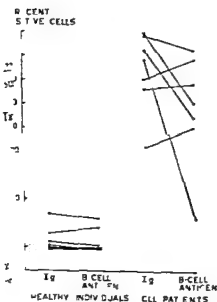


Fig. 1 Peripheral blood lymphocytes in healthy individuals and patients with CLL. Percentage of cells with 7470-B-cell antigen and with sIg (stained with TRITC-labelled Fab<sub>1</sub> fragments of antihuman Fab or TRITC-labelled IgG against human Ig).

Table II Peripheral blood blast cells in patients with AML, AMML, ALL or blast transformation (BT) of CML. % of cells stained with 7470 antiserum

Case no	Diagnosis	Positive cells (%)
1	AML	<0.5
2	AML	<0.5
3	AML	6.5
4	AML	5.5
5	AML	10
6	AMML	2.5
7	AMML	4.0
8	BT of CML	34.0
9	BT of CML	47.0
10	BT of CML	3.0
11	ALL	7.0

### Chronic lymphocytic leukaemia

In CLL the majority of peripheral blood lymphocytes carried the B-cell antigen (Table I). Staining for sIg was performed in 7 cases. A difference was sometimes observed between the number of sIg and B-cell antigen positive cells (Fig. 1). Staining with anti kappa and anti lambda antisera disclosed a monoclonal proliferation in all 7 cases.

### Acute leukaemia

The majority of blasts from the peripheral blood of patients with acute leukaemia or AMML were negative (Table II). In many cases, however, a minority of the blasts were clearly positive (1/7%) and a portion of the others stained very faintly (classified as negative). In 2 of 3 cases of blast transformation of CML a large proportion of the blasts were positive. In one case of acute lymphocytic leukaemia only 5% of the blasts were positive while 89% carried T-cell marker. In all other cases of acute leukaemia the cells lacked sIg or receptor for sheep erythrocytes. The cells from the patients with AMML carried Fc receptors detected by rhodamine-conjugated aggregated human IgG.

### Hairy cell leukaemia

In both patients a large proportion of the hairy cells carried Fc receptors as demonstrated by their ability to bind aggregated human IgG (Table III). The number of cells with receptor for sheep red blood cells (SRBC) was low and in general these cells had

Table III Surface markers and phagocytic capacity of circulating hairy cells in leukaemic reticuloendotheliosis

Case no	Mononuclear cells		Hairy cells (%) with receptor for		
	$\times 10^3/\text{fl}$	Hairy cells (%)	SRBC (E rosettes)	Fc (aggregated IgG)	Phagocytizing hairy cells
1	4.6	74	<1	91	n.t.
2	1.5	32	27*	81	76

Per cent of all mononuclear cells

n.t. = Not tested

the appearance of small lymphocytes though morphological classification of the rosetting cell was sometimes difficult. In the only case examined 76% of the hairy cells phagocytized latex particles but the number of ingested particles was smaller than in mature monocytes and the possibility that they had been adsorbed to the cells could not be entirely excluded. In both cases the majority of the hairy cells carried 7420-B-cell antigen as well as sIg (Table IV). In case 1 only mu and lambda chains were detected while immunoglobulin chains of the four major classes were found in case 2 even if the staining with anti alpha and anti lambda was weak and the number of IgG positive cells was low. When the staining was performed with F(ab')<sub>2</sub> fragments anti kappa and anti lambda antisera only kappa chains were detected.

## DISCUSSION

The antigen(s) identified by 7420 antiserum was detected on normal peripheral blood B lymphocytes and on lymphocytes from patients with CLL, a monoclonal proliferation of B lymphocytes (1, 28). It was also present on the blasts from 2 of 3 cases of

blast transformation of CML. This distribution is similar to that of Ia like antigens. On the contrary only a minority of normal peripheral blood monocytes and blasts from patients with acute myelocytic leukaemia or AMML were positive and staining was weak. No case of ALL of non T or B type was examined. This distribution profile differs from that reported for Ia like antigens. Similar results have been reported by others using rabbit antisera against whole CLL lymphoblastoid cell line or monkey B-cells. A negative reaction with monocytes was obtained in 2 of 3 reports (2, 8, 11) and negative reactions with AML cells in 3 of 3 reports (9, 10, 21). The reason for these differences is not quite clear. It is possible that antisera produced against whole cells after the necessary absorption are so weak that small amounts of antigen cannot be detected. In fact studies using the fluorescence activated cell sorter have demonstrated much smaller amounts of Ia like antigen on AML cells and monocytes than on ALL cells. Cells from blast transformation of CML and B lymphocytes. Only 20% of monocytes were weakly positive and so AML cases were completely negative (23). It is however equally possible that antisera raised

Table IV Surface Ig and 7420-B cell antigen on circulating hairy cells in two cases of leukaemic reticuloendotheliosis

Case no	Hairy cells stained with FITC-labelled IgG against Ig chains (%)						Hairy cells stained with FITC-labelled F(ab') <sub>2</sub> fragments of IgG against Ig chains and 7420-B-cell antigen (%)			
	$\alpha$	$\mu$	$\gamma$	$\delta$	$\kappa$	$\lambda$	$\mu$	$\kappa$	$\lambda$	7420
1	<1	89	1	n.t.	<1	97	96	n.t.	97	94
2	88	76	10	89	95	84	n.t.	88	<1	92

\* Faint staining

n.t. = Not tested

unst whole B lymphocytes may detect antigen other than Ia like antigens. In fact this seems to be the case with the 7420 antiserum since inhibition and capping experiments clearly indicate that the antigen detected is different from Ia like antigen. The cell antigen not identical with Ia like antigen was also reported by Balch et al (2, 3) using an anti-key B cell serum.

The nature and origin of the hairy cells in leukaemic reticuloendotheliosis are controversial. They have been considered to be of B lymphocyte origin, belong to the monocyte-histiocyte series or to be unique cells differing structurally as well as functionally from B lymphocytes as well as monocytes. The arguments in favour of these hypotheses have recently been reviewed by Catovsky (12) and have since then been the subject of several reports (11, 13, 16, 17, 18, 26, 29, 30, 31, 38). In the two cases presented here the cell surface marker studies suggest a near relation of the hairy cells to lymphocytes. The cells were clearly stained with the 7420 antiserum which gave only a weak staining of a minority of normal monocytes and failed to act with the monocytoid cells from two cases of MML. The slg was clearly monoclonal in case 1 and when stained with F(ab')<sub>2</sub> fragments only one light chain type was detected in case 2. It seems that preincubation at 37°C was sufficient to remove most of the IgG which was probably bound in vivo to Fc receptors. A receptor for the Fc part of IgM has recently been found on hairy cells (11) and it cannot be completely excluded that the IgM detected was adsorbed to the cell surface. This seems however very unlikely since only one light chain type was found and there was no evidence of a monoclonal Ig in plasma or urine. The nature of the staining for IgD and the weak staining for IgA cannot be determined since F(ab')<sub>2</sub> fragments of these antisera were not available.

While the finding of Ig with restricted heterogeneity on hairy cells has been reported several times (7, 12, 13, 17, 18) we have not found any reports on the occurrence of B-cell antigen defined by anti-CLL antisera. Four cases have been examined with antisera against Ia like antigens which have also been found on the cells (5, 13, 37).

#### ACKNOWLEDGEMENTS

This work was supported by grants from Thorsten and Elsa Segerfalk's Foundation, Alfred Österlund's Foun-

dation, the Medical Faculty of the University of Lund and Cancer Research Funds of Malmö General Hospital.

#### REFERENCES

- 1 Aisenberg A C & Bloch K J. Immunoglobulins on the surface of neoplastic lymphocytes. *N Engl J Med* 287: 272, 1972.
- 2 Balch C M, Dougherty P A & Vogler L. Cross reacting anti-monkey lymphocyte antisera: A simplified immunofluorescence approach for detecting human T and B lymphocytes. *J Surg Res* 22: 636, 1977.
- 3 Balch C M, Dougherty P A, Vogler L & Cresswell P. Fluorescent detection of a human B cell differentiation antigen (Ag) on normal and neoplastic lymphocytes. *Fed Proc* 36: 1317, 1977.
- 4 Berntorp E, Tureson I & Zettervall O. Heterologous B-cell antisera may detect non Ig non HLA DR antigens. *Scand J Immunol*. In press, 1979.
- 5 Billing R, Rafizadeh B, Drew I, Hartman G, Gale R & Teraski P. Human B lymphocyte antigens expressed by lymphocytic and myelocytic leukaemia cells. I. Detection by rabbit antisera. *J Exp Med* 144: 167, 1976.
- 6 Billing R, Ting A & Teraski P. Human B lymphocyte antigens expressed by lymphocytic and myelocytic leukemia cells. II. Detection by human anti B cell alloantisera. *J Natl Cancer Inst* 58: 199, 1977.
- 7 Braylan R C, Jaffe E S, Triche T J, Nanba K, Fowlkes B J, Metzger H, Frank M M, Dolan M S, Yee C L, Green I & Berard C W. Structural and functional properties of the hairy cells of leukemic reticuloendotheliosis. *Cancer* 41: 210, 1978.
- 8 Brochier J, Abou Hamed Y A, Gueho J P & Revillard J P. Study of human T and B lymphocytes with heterologous antisera. I. Preparation, specificity and properties of antisera. *Immunology* 31: 749, 1976.
- 9 Brouet J C, Velenski F, Daniel M T, Flandrin G, Preudhomme J L & Selgmann M. Immunological classification of acute lymphoblastic leukaemias. Evaluation of its clinical significance in a hundred patients. *Br J Haematol* 33: 319, 1976.
- 10 Brown G & Greaves M F. Expression of human T and B lymphocyte cell surface markers on leukaemic cells. *Lancet* 2: 753, 1974.
- 11 Burns G F, Cawley J C, Barker C R, Goldstone A H & Hayhoe F G J. New evidence relating to the nature and origin of the hairy cell of leukaemic reticuloendotheliosis. *Br J Haematol* 36: 71, 1977.
- 12 Catovsky D. Hairy cell leukaemia and prolymphocytic leukaemia. *Clin Haematol* 6: 245, 1977.
- 13 Cawley J C, Burns G F, Nash T A, Higgy K E, Child J A & Roberts B E. Hairy-cell leukemia with T-cell features. *Blood* 51: 61, 1978.
- 14 Forsum U. Characterization of FITC labelled F(ab')<sub>2</sub> fragments of IgG and a rapid technique for the separation of optimally labelled fragments. *J Immunol Methods* 2: 183, 1972.
- 15 Geier S S & Creswell P. Rabbit anti-

- B cell allo-antigens Effects on the mixed lymphocyte response *Cell Immunol* 28 341 1977
- 16 Golde D W Stevens R H Quan S G & Saxon A Immunoglobulin synthesis in hairy cell leukaemia *Br J Haematol* 35 359 1977
  - 17 Golomb H M Vardiman J Sweet D L Simon D & Variakojis D Hairy cell leukaemia Evidence for the existence of a spectrum of functional characteristics *Br J Haematol* 38 161 1978
  - 18 Gordon J Smith J L & Roath S Free immunoglobulin in light chain synthesis by neoplastic cells from six cases of leukaemic reticuloendotheliosis *Br J Haematol* 39 150 1978
  - 19 Greaves M F & Brown G A human B lymphocyte specific antigen *Nature New Biology* 246 116 1973
  - 20 Hymans W Schuit H R E & Hulsing Hesselink E An immunofluorescence study on intracellular immunoglobulins in human bone marrow cells *Ann NY Acad Sci* 177 290 1971
  - 21 Hsu C C S Marti G E & Mittal K K Antisera against leukaemia associated antigens on human lymphocytes *Clin Exp Immunol* 27 487 1977
  - 22 Humphreys R E McCune J M Chess L Herrman H C Malenka D J Mann D L Parham P Schlossman S F & Strominger J Isolation and immunologic characterization of a human B-lymphocyte-specific cell surface antigen *J Exp Med* 144 98 1976
  - 23 Janossy G Goldstone A H Capellaro D Greaves M F Kulenkampff J Pippard M & Welsh K Differentiation linked expression of p 28 33 (Ia like) structures on human leukaemic cells *Br J Haematol* 37 391 1977
  - 24 Kaplow L S Myeloperoxidase stains *Am J Clin Pathol* 63 451 1975
  - 25 Klareskog L Tragårdh L Lindblom J B & Peterson P A Reactivity of a rabbit antiserum against highly purified HLA DR antigens *Scand J Immunol* 7 199 1978
  - 26 Matre R Talstad I & Haugen Å Surface markers in non phagocytic hairy cell leukemia *Acta Pathol Microbiol Scand (C)* 85 406 1977
  - 27 Pattengale P K & Reichelderfer P S Stabilization of sheep red blood cell (E) rosettes with high molecular weight compounds *Immunol Commun* 4 179 1975
  - 28 Preud'homme J L & Seligmann M Surface bound immunoglobulins as a cell marker in human proliferative diseases *Blood* 40 777 1972
  - 29 Rieber E P Linke P R Reithmüller I Heyden H W & Waller D W Fc Reiz und Oberflächenimmunoglobuline auf Zell Haarzell Leukämie *Blut* 32 269 1976
  - 30 Saxon A Stevens R H Quan S G & D W Immunologic characterization of hairy leukemias in continuous culture *J Immunol* 1978
  - 31 Scheinberg M Brenner A I Sullivan Catchcart E S & Katayama I The heterogeneity of leukemic reticuloendotheliosis hairy leukemia *Cancer* 37 1302 1976
  - 32 Schlossman S F Chess L Humphreys Strominger J L Distribution of Ia like molecules on the surface of normal and leukemic human cells *Natl Acad Sci USA* 73 1288 1976
  - 33 Snary D Barnstable C J Bodmer W F Low P N & Crumpton M J Cellular differentiation and molecular nature of human antigens *Scand J Immunol* 6 439 1977
  - 34 Sullivan A K Jerry L M Rowden G M Expression of a B lymphocyte antigen on lymphocytic and other leukemias *Clin Immunopathol* 8 64 1977
  - 35 Turesson I Distribution of immunoglobulin producing cells in bone marrow and lymphoid tissues treated with monoclonal gammopathy *Acta Scand* 203 247 1978
  - 36 Winchester R J Ross G D Jarowski C C Y Halper J & Broxmeyer H E Expression of Ia-like antigen molecules on human granulocytes in early phases of differentiation *Proc Natl Acad Sci USA* 74 4012 1977
  - 37 Winchester R J Wang C Y Halper Hoffman T Studies with B-cell allo-antigens. Parallel reactivity and special properties *Scand J Immunol* 5 745 1976
  - 38 Winkelstein A Zidar B L Smith W L Duck R K Zeigler Z R Rabin B S W T L Lee R E & Krause J R Cellular characteristics of hairy cell leukemia *Clin Res* 24 3
  - 39 Zighelboim J Bich A & Durantez A Reactivity of human and rabbit sera of common anti leukemia blast cells peripheral blood B lymphocytes and monocytes *Cancer Res* 37 3656 1977

# The Expression of a Human B-Lymphocyte Antigen and Surface Membrane Immunoglobulin by Lymphoid cells from Patients with Lymphocytic Lymphoma, Multiple Myeloma and Benign Monoclonal Gammopathy

Ingemar Turesson Enk Berntorp and Olle Zettervall

*From the Department of Internal Medicine University of Lund Malmö General Hospital Malmö Sweden*

**STRACT** Lymphoid cells from patients with lymphocytic lymphoma, multiple myeloma or benign monoclonal gammopathy (BMG) were examined by indirect immunofluorescence for the expression of surface membrane immunoglobulin (sIg) and B-cell antigen defined by a rabbit antiserum against chronic lymphocytic leukaemia lymphocytes. This antiserum has been shown to detect a B cell antigen different from Ia like antigen. In well differentiated lymphocytic lymphoma, the cells carried the B-cell antigen well as one class of heavy and light Ig chain. A circulating monoclonal lymphocyte population was regularly found in the blood although the lymphocyte number was not increased. In multiple myeloma the number of circulating cells carrying mu chains was all the depression being most pronounced in patients who had been treated with cytostatics. A monoclonal population of lymphocytes expressing the isotype(s) of the M component was found in the blood in 6/15 cases and more often in patients with advanced disease. The number of cells with B cell antigen agreed fairly well with the number of Ig positive cells indicating that the B cell antigen was expressed on normal as well as myeloma related lymphocytes. A dissociation of the expression of the antigen was however observed in two cases (one lymphocytic lymphoma, one myeloma) with a large number of cells with B-cell antigen but a small number of cells with sIg. The B-cell antigen was usually not detected on the surface membrane of Ig-containing plasma cells from patients without monoclonal gammopathy from the majority of patients with BMG but on a varying proportion of myeloma cells. The tentative conclusion is drawn that the B-cell antigen is a differentiation antigen which is gradually lost during B-lymphocyte differentiation but is retained to some extent on myeloma cells as an expression of a lower degree of maturity.

**Key words** B-cell antigen surface membrane immunoglobulin myeloma benign monoclonal gammopathy lymphoma

Acta Med Scand 206 37 1979

Chronic lymphocytic leukaemia (CLL) and most cases of lymphocytic lymphoma are B-cell proliferations where the majority of the cells are frozen at the maturation level of B lymphocytes (2, 21). A minor part of the malignant clone may mature to immunoglobulin secreting cells and in such cases a monoclonal spike usually of IgM type is found in the plasma (21, 27). Multiple myeloma and benign monoclonal gammopathy (BMG) are B-cell proliferations where the majority of the cells have matured to Ig secreting cells and an M-component in plasma and/or urine is found with few exceptions. According to several reports the malignant clone is however also represented at the B lymphocyte level (1, 7, 13, 18, 21). B-cell antigens defined by heterologous antisera against whole B-cells or B cell membrane products (Ia like antigens) are readily demonstrated on the surface of lymphocytic lymphoma

**Abbreviations** CLL=chronic lymphocytic leukaemia BMG=benign monoclonal gammopathy WDL=well differentiated lymphocytic lymphoma DWDL=diffuse WDL NWDL=nodular WDL DPDL=diffuse poorly differentiated lymphocytic lymphoma DHL=diffuse histiocytic lymphoma FITC=fluorescein-isothiocyanate TRITC=tetramethyl rhodamine-isothiocyanate sIg=surface membrane immunoglobulin PBS=phosphate-buffered saline BSA=bovine serum albumin IFL=immunofluorescence k/l ratio=the ratio of kappa positive to lambda-positive cells



phoma cells (14-16) whereas conflicting results are reported regarding the expression of B-lymphocyte antigens on the surface of plasma cells (3, 6, 11, 24).

We have recently reported on a heterologous antiserum against CLL cells that identifies a B-cell specific antigen not identical with Ia-like antigen (5, 28). The present report concerns the distribution of this antigen on lymphocytic lymphoma cells as well as on normal and malignant plasma cells. We also report on the occurrence of circulating monoclonal B-lymphocyte populations in the peripheral blood in patients with lymphocytic lymphoma and multiple myeloma.

## STUDY POPULATION

**Healthy individuals** This group consisted of 10 members of the laboratory staff. Only peripheral blood mononuclear cells were examined.

**Myeloma** All 24 patients had an M-component in plasma and/or monoclonal light chains in the urine and subnormal levels of at least one Ig class. They also fulfilled at least one of the following criteria:  $\geq 10\%$  plasma cells in a bone marrow smear or osteolytic lesions demonstrated by X-ray examination. The M-component was of IgG type in 12 cases, IgA in 6, IgD in 2 and only light chains in 4 cases. Bone marrow and peripheral blood were examined in 6 patients, blood only in 9 and bone marrow only in 9. Ten patients were examined before treatment and 14 had been on cytostatics. Clinical stage was estimated according to  $\Sigma$  and Salmon (8).

**IgM monoclonal gammopathy** All 8 BMC patients had an M-component in plasma with or without small amounts of monoclonal light chains in the urine but no osteolytic lesions at X-ray examination. There was no change or a very slow progress in M-component concentration (i.e. an increase of at most 2 g/l per year) during an observation time of at least two years (mean 59 months). The M-component was of the IgG type in 5 patients and of the IgA type in 3.

**Malignant lymphoma** Seven of 9 patients had well differentiated lymphocytic lymphoma (WDL). In three of these it was diffuse (DWDL), in one nodular (NWDL) and in three cases no further classification was made. One patient had diffuse poorly differentiated lymphocytic lymphoma (DPDL) and one diffuse histiocytic lymphoma (DHL) according to the classification of Rappaport. Eight patients had bone marrow involvement. Lymphoma tissue (bone marrow, lymph node or spleen) was examined in 4 patients and peripheral blood in 8.

## METHODS

**Antisera** An anti-B-cell serum (7420) was raised in one rabbit by immunization with lymphocytes from a patient with CLL. The preparation of FITC (fluorescein isothiocyanate)-labelled F(ab)<sub>2</sub> fragments of IgG an-

tiserum absorptions and testing for B-lymphocyte specificity have been described earlier (5). FITC F(ab)<sub>2</sub> fragments of IgG from normal rabbit prepared according to the same procedure.

FITC-labelled antisera against alpha mu gamma delta heavy chains TRITC (tetramethyl rhodamine isothiocyanate)-labelled polyvalent antiserum against human Ig heavy and light chains and TRITC<sup>11</sup> F(ab)<sub>2</sub> fragments of goat antihuman Fab were from Nordic Immunological Laboratories, Tübingen, Netherlands. FITC-labelled antisera against kappa lambda light chains were from Dakopatts, Copenhagen, Denmark. The specificity of the conjugate was tested by myeloma and macroglobulinaemia bone marrow smears described earlier (27). To stain all cells with surf-brane Ig (sIg) the TRITC-labelled polyvalent which was used in the early phase of the study and the FITC-labelled F(ab)<sub>2</sub> fragments were used later. Since interference was observed in sIg positive cells in health individuals they are not reported separately.

**Preparation of cells** Mononuclear cells were taken from heparinized venous blood by the Ficoll-met method. They were suspended in PBS (phosphate buffered saline, pH 7.2) containing 1% BSA (bovine albumin) at a concentration of  $4 \times 10^6$ /ml and kept water-bath at 37°C for 45 min. After washing twice prewashed PBS-BSA the cells were suspended in BSA for immunofluorescent (IFL) staining.

Bone marrow was aspirated from the sternum iliac crest and a single-cell suspension was described earlier (26). The cells were incubated at 4°C for 45 min as described above. Cytocentrifuge smears made from each cell suspension for intracellular sIg. Single-cell suspensions from lymph nodes or spleen obtained by fine needle aspiration or by grinding material through a Borel press.

## Immunofluorescence

**Peripheral blood mononuclear cells** One drop (approximately 30  $\mu$ l) of the cell suspension containing cells was mixed with one drop of the FITC or conjugate in plastic tubes. These were incubated for 30 min with intermittent shaking. The cell washed twice with PBS-BSA at +4°C and mounted in buffered glycerol, pH 7.8. The slides were examined with a Leitz Orthoplan fluorescence microscope equipped with illumination and filter systems for narrow band emission of FITC and TRITC (12). The cells were first identified in phase contrast with transmitted light and then examined for membrane fluorescence with incident light. Two hundred cells with the typical morphology of lymphocytes were examined and the percentage of fluorescent cells was calculated. In the lymphoma patients larger lymphoid cells were sometimes more abundant and were included.

**Bone marrow cells** One drop of the cell suspension containing 150 000 cells was mixed with one drop conjugate (FITC-labelled F(ab)<sub>2</sub> fragments of 7420 antiserum or of normal rabbit IgG). After incubation and washing as described above, cytocentrifuge slides prepared, the cells were fixed in acetone at -20°C for 1 min and stained for intracellular Ig using a poly-

Table 1 Peripheral blood lymphocytes in patients with malignant lymphoma: percentage of cells with sIg and with 7420 B cell antigen

Case	Diagnosis	Stage	M-component		Lymphocytes ( $\times 10^9/l$ )	Percentage of lymphocytes stained with antisera against		
			Type	Concentration (g/l)		$\kappa$	$\lambda$	7420 B cell antigen
1	DHL	IA	GK	6	0.8	5.0	3.0	7.5
2	DWDL	IVA	GK	24	3.8	<1.0	<1.0	33.0
3	DWDL	IVA	Mk	10	3.5	3.3	0.5	6.5
4	WDL	IVB	Mk	4	1.9	31.0	3.5	36.0
5	DPDL	IVB	Mk	8	5.7	79.0	0.5	44.0
6	WDL	IVA	ML	11	1.1	0.5	4.5	5.0
7	WDL	IVB	-	-	0.6	35.5	<0.5	30.0
8	DWDL	IVA	-	-	3.0	45.0	2.0	40.5
9	NWDL	IVA	-	-	11.0	19.0	1.0	28.0
Healthy individuals (N=7)					1.4-4.0	8.2	4.2	12.5

\*ITC labelled antiserum against human Ig heavy and light chains (26). The slides were washed and mounted in glycerol. They were examined first in TRITC fluorescence to identify cells with a homogeneous intracytoplasmic fluorescence and plasmacytoid morphology and then in FITC fluorescence to identify cells with surface fluorescence. Two hundred Ig-containing cells were examined and the percentage of surface stained cells was calculated.

#### b. T cell stimulation

Peripheral blood mononuclear cells from one healthy individual were cultured in medium RPMI 1640 together with phytohemagglutinin (PHA) strain Cowan 1 as described elsewhere (4). The cultures were provided by G. Banck, Department of Bacteriology, Malmö General Hospital. After 4-5 days culture the cells were spun down, washed several times in PBS-BSA and stained with FITC labelled F(ab)<sub>2</sub> fragments of 7420 antiserum as described above.

## RESULTS

### a. Malignant lymphoma

In three patients with WDL and bone marrow involvement the majority of bone marrow lymphoid cells were stained with 7420 antiserum and by either anti kappa or anti lambda antiserum indicating a monoclonal proliferation. The number of 7420 positive cells agreed fairly well with the number of sIg positive cells. Similar results were obtained with cell suspensions from a lymph node and spleen from one patient each. In the peripheral blood staining for sIg disclosed a monoclonal lymphocyte population, i.e. the ratio of kappa positive to lambda positive cells (k/λ ratio)  $\geq 4.0$  or  $\leq 0.5$  (normal range 1.3-2.6) in 6 of 7 cases of WDL or

PDL but not in the patient with DHL (Table 1). The number of 7420-positive cells agreed in general well with the number of Ig positive cells (Fig. 1). One patient with a very low number of sIg positive cells (1%) had a high percentage of 7420-positive cells (33%).

### Multiple myeloma

In multiple myeloma the number of sIg positive peripheral blood lymphocytes varied widely, the mean value being somewhat lower than in healthy

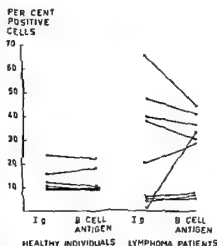


Fig. 1 Peripheral blood lymphocytes in healthy individuals and patients with malignant lymphoma. Percentage of cells with 7420-B-cell antigen and with surface membrane Ig (stained with TRITC labelled F(ab)<sub>2</sub> fragments of anti Fab or with TRITC labelled polyvalent IgG against human Ig).

Table II Peripheral blood lymphocytes in healthy individuals and patients with multiple myeloma: percentage and absolute number of cells with 7420 B cell antigen and with sIg<sub>k</sub> (stained with fragments of anti Fab or with anti mu)

		B-cell antigen positive lymphocytes		sIg positive lymphocytes stained with antiserum against					
				Fab <sup>a</sup>		mu			
		%	× 10 <sup>6</sup> /l	%	× 10 <sup>6</sup> /l	%	× 10 <sup>6</sup> /l	%	× 10 <sup>6</sup> /l
Healthy individuals	Mean	12.5	246	12.7	249	10.2	198		
	Range	9-22	156-403	9-23.5	147-431	7.5-14.5	134		
	N	10	7	10	7	7	7		
Multiple myeloma untreated	Mean	10.2	209	9.7	190	7.0	149		
	Range	5-15	95-298	4-13.5	67-269	4-11.5	75		
	N	7	6	7	6	6	6		
Multiple myeloma treated	Mean	8.1	208	5.8*	88*	2.4**	36		
	Range	3.5-27	10-875	1-20	9-458	1-3.5	1*		
	N	8	8	8	8	7	7		

\* $p < 0.05$  \*\* $p < 0.001$

Whole IgG against human Ig heavy and light chains was used in some early cases

individuals (Table II). This difference was more pronounced in patients who had been treated with cytostatics. They had a significant depression of the number of sIg positive lymphocytes ( $p < 0.05$ ). In 6 of 15 cases (3 untreated, 3 treated with cytostatics) there was an imbalance in the k/l ratio with the majority of B lymphocytes carrying the same class of light chain as that of the M component (Table II).

The number of sIg positive lymphocytes increased substantially in only one of these six cases (Fig. 2). An abnormal k/l ratio was seen more often in patients with myeloma of clinical stage III (5/7) than among those with clinical stage II (1/8). No patient with myeloma of clinical stage I was examined.

In 3 patients (nos. 2, 4, 5) the majority of the lymphocytes also carried the same class of heavy chain as that of the M component. In 2 patients (nos. 2, 4) lymphocytes carrying mu chains were found, but several cells carried the heavy chain of the M-component and might well be responsible for the change in the k/l ratio. As double staining was not performed, it cannot be determined whether lymphocytes carrying mu chains were restricted to mainly or lambda chains.

The number of B-cell antigen positive cells was also somewhat smaller in myeloma patients than in healthy individuals. The difference was more pronounced than with sIg positive lymphocytes.

Table III Peripheral blood lymphocytes in patients with multiple myeloma and a monoclonal distribution of sIg positive cells: percentage of cells carrying Ig heavy and light chains and 7420 B cell antigen. Cases 1-3 were examined before treatment.

Case no.	M-component heavy and light chain	Percentage of lymphocytes stained with antisera against						
		κ	λ	α	μ	γ	ε	7420
1	GK	10.0	1.0	nt	nt	nt	nt	11.0
2	AK	8.5	2.0	10.5	3.5	1.0	nt	12.0
3	AK	4.0	1.0	2.0	5.0	1.0	nt	6.0
4	GL	2.0	6.0	1.0	2.0	8.0	nt	6.0
5	DL	2.0	21.0	1.0	2.5	0.5	21.0	27.0
6	GK	5.5	1.0	0.5	3.0	1.5	nt	4.5
Healthy individuals (N=7)		8.2	4.2	2.3	10.2	0.7		12.5

nt = Not tested

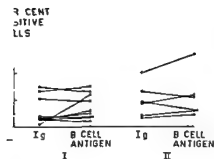


Fig. 2 Peripheral blood lymphocytes in patients with multiple myeloma. Percentage of cells with 7420 B-cell antigen and with sIg (stained with TRITC labelled F(ab)<sub>2</sub> fragments of anti Fab or with TRITC labelled polyvalent G against human Ig). I=patients with a k/λ ratio of 0.8-1.0 II=patients with k/λ ratio of <0.3 or ≥4.0

statistically insignificant. In most cases there was no agreement between the number of sIg positive cells but one exception was noted (Fig. 2). In this case the number of B cell antigen positive cells (7%) exceeded considerably the number of sIg positive cells (1%). This patient had multiple myeloma of stage III.

Bone marrow plasma cells from patients without monoclonal gammopathy or lymphoproliferative disease did not carry the B-cell antigen (Fig. 3). In patients with BMG the number of positive plasma cells was also mostly small with some exceptions.

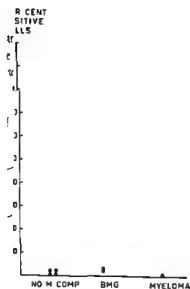


Fig. 3 Ig-containing bone marrow plasma cells in patients with multiple myeloma, BMG or without an M-component. Percentage of cells with 7420-B-cell antigen.

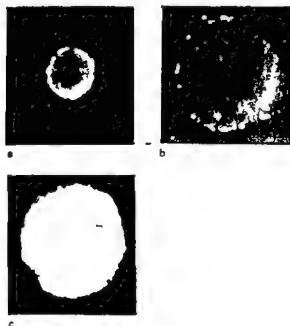


Fig. 4 A small lymphocyte (a) and a plasma cell (b) stained in suspension with FITC labelled F(ab)<sub>2</sub> fragments of 7420 antiserum and examined in FITC fluorescence. The same plasma cell is also seen after fixation (c) staining for intracellular Ig with TRITC labelled anti Ig and examination in TRITC fluorescence. Kodak Tri X Pan×1250.

In contrast, the antigen was expressed on the membrane of a varying proportion of plasma cells from patients with multiple myeloma. Although some myeloma cases were negative and considerable overlapping was observed, the number of positive cells in myeloma patients differed significantly from that in patients with BMG ( $p < 0.01$ ) or without an M-component ( $p < 0.005$ ). The fluorescence pattern of the myeloma cells was clearly different from that of B lymphocytes. While these had a distinct homogeneous confluent membrane fluorescence, the positive plasma cells were very weakly stained with a sparse granular fluorescence (Fig. 4). In the two cases of BMG with a large number of B-cell antigen positive cells, less than 2% of plasma cells containing light chains of another class than that of the M-component carried the B cell antigen. Such studies were not performed on the plasma cells from myeloma patients.

#### Mitogen stimulated peripheral blood lymphocytes

In 4, 5 and 7 day cultures of peripheral blood mononuclear cells together with the mitogen



number of bone marrow plasma cells containing Ig other classes than that of the M-component (??) seems that the depression of other clones is at least partly expressed already at the B lymphocyte level. On the other hand, a circulating population of lymphocytes which express the idiotype of the M-component exists in most cases of myeloma. Some of them seem not to react readily with anti-idiotypic antisera but some probably do, as in some myeloma cases the lymphocytes express predominantly k or l chains. Such monoclonal lymphocyte populations may be more common in patients with advanced disease. In this connection the results with 7470 antiserum might be of some interest. In general there was a good agreement between the number of sIg positive lymphocytes and the B-cell antigen positive cells in polyclonal as well as in monoclonal cases, indicating that both the normal and the myeloma related lymphocytes carry the antigen. In one case the number of B-cell antigen positive lymphocytes exceeded considerably the number of sIg positive. It is tempting to speculate that they might correspond to the cells carrying the type of Ig or to those carrying C<sub>3</sub> receptor but not Ig (20). Such a dissociation between B cell antigen and sIg positive cells was also observed in one patient with lymphocytic lymphoma. The opposite might also occur as in some cases of CLL and lymphocytic lymphoma with a smaller number of cell antigen than sIg positive lymphocytes.

The B cell antigen was found on a large number of blasts obtained on stimulation of peripheral blood lymphocytes with Cowan Staphylococci, a selective B-cell mitogen (4, 9, 22) but it was usually not detected on the surface of normal plasma cells or myeloma cells from most cases of BMG. It seems therefore to be a differentiation antigen that is lost during full maturation to Ig secreting plasma cells. The weak expression of the antigen on some but not all myeloma cells is consistent with a less complete differentiation. In fact myeloma cells are known to have a more immature nuclear chromatin structure than plasma cells from patients with BMG without M-component (10, 25). It should be emphasized that in both myeloma and BMG the majority of the bone marrow plasma cells belong to the M-component forming clone as demonstrated by intracellular staining for k and l light chains (??). In the present series the number of plasma cells belonging to other clones could be roughly estimated from the k/l ratio to less than 5% in the

myeloma cases and to 3–30% in the BMG cases. Even if the assumption is made that only 70% of the Ig containing cells in BMG belong to the M-component producing cell clone and that all B cell antigen positive cells observed belong to this clone the percentage of positive cells in the clone is still significantly lower than in multiple myeloma.

The presence of B-cell antigen on myeloma cells has also been reported by others (3, 6) using antisera raised against CLL lymphocytes and monkey spleen B-cells respectively. Normal plasma cells were not examined in these reports. Others have failed to demonstrate B-cell antigen on myeloma cells using antisera against B-cell membrane proteins—lambda like antigen—(11, 24) although the antigen was detected on mitogen induced plasma cells (11). Although lambda like antigen also might be considered as a B cell differentiation antigen in the B lymphocyte series its cellular distribution is thus different from the B-cell antigen detected by 7470 antiserum.

#### ACKNOWLEDGEMENTS

This work was supported by grants from Thorsten and Elsa Segerfalk's Foundation, Alfred Österlund's Foundation, the Medical Faculty of the University of Lund and Cancer Research Funds of Malmö General Hospital.

#### REFERENCES

1. Abdou N I & Abdou N L. The monoclonal nature of lymphocytes in multiple myeloma. *Ann Intern Med* 83: 47, 1975.
2. Aisenberg A G & Long J C. Lymphocyte characteristics in malignant lymphoma. *Am J Med* 58: 300, 1975.
3. Balch C M, Dougherty P A & Vogler L. Distribution and immunocytometric properties of a unique B-cell differentiation antigen on human leukaemic lymphocytes. *Proc Am Assoc Cancer Res* 19: 119, 1978.
4. Banck G & Forsgren A. Many bacterial species are mitogenic for human blood B lymphocytes. *Scand J Immunol* In press, 1979.
5. Berntorp E, Turesson I & Zettervall O. Heterologous B-cell antisera may detect non Ig non HLA DR antigens. *Scand J Immunol* In press, 1979.
6. Brown G & Greaves M F. Expression of human T and B lymphocyte cell surface markers on leukaemic cells. *Lancet* 2: 753, 1974.
7. Chen Y, Bhoopalani N, Yakus V & Heller P. Changes in lymphocyte surface immunoglobulin in myeloma and the effect of an RNA-containing plasma factor. *Ann Intern Med* 83: 625, 1975.
8. Durne B G M & Salmon S E. A clinical staging system for multiple myeloma. *Cancer* 36: 842, 1975.

- 9 Forsgren A, Svedjelund A & Wigzell H. Lymphocyte stimulation by protein A of *Staphylococcus aureus*. *Eur J Immunol* 6: 207, 1976.
- 10 Graham R. C. & Bernier G. M. The bone marrow in multiple myeloma: correlation of plasma cell ultrastructure and clinical state. *Medicine* 54: 225, 1975.
- 11 Halper J, Fu S. M., Winchester R. & Kunkel H. G. Patterns of expression of human "Ia-like" antigens during the terminal stages of B-cell development. *J Immunol* 120: 1480, 1978.
- 12 Hijmans W., Schuit H. R. E. & Hulsing Hesselink E. An immunofluorescence study on intracellular immunoglobulins in human bone marrow cells. *Ann NY Acad Sci* 177: 290, 1971.
- 13 Holm G., Mellstedt H. & Pettersson D. Idiotypic immunoglobulin structures on blood lymphocytes in human plasma cell myeloma. *Immunol Rev* 34: 139, 1977.
- 14 Janossy G., Goldstone A. H., Capellaro D., Greaves M. F., Kulenkampff J., Pippard M. & Welsh J. Differentiation linked expression of p 28/33 (Ia-like) structures on human leukaemic cells. *Br J Haematol* 37: 391, 1977.
- 15 Jones S. V. & McFarlane H. T. B and B cells in myelomatosis. *Br J Haematol* 31: 545, 1975.
- 16 Kadin M. E. & Billing R. J. B lymphocyte antigens in the differential diagnosis of human neoplasia. *Blood* 51: 813, 1978.
- 17 Knapp W., Schuit H. R. E., Bolhuis R. L. H. & Hijmans W. Surface immunoglobulins in chronic lymphatic leukaemia, macroglobulinaemia and myelomatosis. *Clin Exp Immunol* 16: 541, 1974.
- 18 Lindstrom F., Hardy W. R., Eberle B. J. & Williams R. C. Multiple myeloma and benign monoclonal gammopathy: Differentiation by immunofluorescence of lymphocytes. *Ann Intern Med* 78: 837, 1973.
- 19 Lobo P. L., Westervelt F. B. & Horwitz D. A. Identification of two populations of immunoglobulin bearing lymphocytes in man. *J Immunol* 114: 1975.
- 20 Mackenzie M. R. & Pagheroni T. Multiple myeloma: an immunologic profile. I. Peripheral blood studies. *J Immunol* 118: 1864, 1977.
- 21 Preud'homme J. L., Brouet J. C. & Seligmann J. Lymphocyte membrane markers in human lymphoproliferative diseases. In: *Membrane receptors lymphocytes* (ed. M. Seligmann, J. L. Brouet, J. F. Kourilsky) pp. 417-429. North Holland Publishing Co., Amsterdam, 1975.
- 22 Romagnani S., Amadori A., Giudizi M. G. B., Di R. Maggi E. & Ricci M. Different mitogenic activity of soluble and insoluble staphylococcal protein A (SPA). *Immunology* 35: 471, 1978.
- 23 Scheinberg M. A. & Catchcart E. S. Comprehensive study of humoral and cellular immune abnormalities in 26 patients with systemic amyloidosis. *Rheum* 19: 173, 1976.
- 24 Schlossman S. F., Chess L., Humphreys R., Strominger J. L. Distribution of Ia-like molecules on the surface of normal and leukemic human cells. *Natl Acad Sci USA* 73: 1288, 1976.
- 25 Turesson I. Nucleolar size in benign and malignant plasma cell proliferation. *Acta Med Scand* 197: 1975.
- 26 — Distribution of immunoglobulin-containing cells in human bone marrow and lymphoid tissues. *Acta Med Scand* 199: 293, 1976.
- 27 — Distribution of immunoglobulin-containing cells in bone marrow and lymphoid tissues in patient with monoclonal gammopathy. *Acta Med Scand* 200: 1978.
- 28 Turesson I., Berntorp E. & Zettervall O. T. Expression of a human B-lymphocyte antigen on different types of leukaemia. *Acta Med Scand* 1979.

## Electrolytes and Whole Body Potassium in Acute Leukemia

Bo Lantz Björn Carlmark and Peter Reizenstein

*From the Department of Medicine Division of Hematology Karolinska Hospital Stockholm Sweden*

**ABSTRACT** In a consecutive series of 22 patients with acute leukemia the total body potassium was determined in 18 patients on 39 occasions during relapse and remission. Total body water was also determined. A control group consisting of 88 age-matched healthy volunteers was also studied. The patients had a significantly lower mean potassium concentration, per kg body weight, per kg lean body mass and per kg water than the controls ( $p < 0.001$ ). Individually, 11 out of the 18 patients had at least one value below the lower 95% confidence limit. Hypokalemia was frequent both in the patients with relapse (7/11) and normal (3/6) potassium per kg lean body mass. Five of 13 investigated patients showed laboratory indications of secondary hyperaldosteronism, which might be partly responsible for the hypokalemia. Increased serum or urine levels of renin were found in 62% of the patients.

**Keywords:** acute leukemia, electrolytes, whole body potassium.

*Acta Med Scand* 206: 45-50, 1979.

Previous studies have demonstrated that hypokalemia occurs in acute leukemia (17, 23). Renin (27) and nephrotoxic or sodium retaining drugs (28) have been suggested as probable causes of the hypokalemia. Other disturbances of electrolyte and water metabolism have also been described (3, 14, 18, 21, 25, 39, 40). The purpose of the present paper is to study whether hypokalemia in acute leukemia is accompanied by a potassium depletion. Previously only anecdotal information has been available concerning total body potassium in leukemia (29). Preliminary results of this study have been reported earlier (19).

## SUBJECTS AND METHODS

Twenty-one patients with acute non-lymphatic leukemia and one patient with acute lymphatic leukemia were

studied during 1974-75. Eighteen patients were in the initial phase of leukemia. 4 had been in remission and had relapsed (Table 1). Electrolyte studies were not included if they had been carried out during a period with increased serum creatinine.

## Treatment

As initial cytostatics, rubidomycin and cytosine arabinoside were given except to patients over 70 years of age, who received the latter combined with thioguanine. Treatment schedules have been prescribed in a previous publication (35). Patients not studied in the initial phase of disease (nos. 4, 5, 6 and 19) had received prednisolone in addition. If these combinations failed, other cytostatics were used: vincristine, methotrexate, 6-mercaptopurine and prednisolone (VAMP), cyclophosphamide, vincristine, cytosine arabinoside and prednisolone (COAP), and in some patients, especially those 4 with acute promyelocytic leukemia, a renewed trial with rubidomycin.

## Controls

A group of 88 apparently healthy volunteers, aged 20-94 years and weighing 48-104 kg, served as controls for the whole body potassium study. They were divided into four subgroups: male and female, under and over 50 years of age.

## Total body potassium

The total body potassium was estimated in a whole body counter (31) by measuring the 1.46 MeV  $\gamma$  rays emitted by  $^{40}\text{K}$ , which forms 0.12% of naturally occurring potassium. The counter was calibrated with phantoms containing KCl and an overall error of 7.2% was found for a single measurement with a reproducibility of 5.1%. One measurement of  $^{40}\text{K}$  was performed in 18 of the patients and 2 or 3 measurements in 14. All except 3 patients were measured within 2 months from admission.

**Body composition measurement.** The total body fat was estimated from an experimentally derived equation relating the subcutaneous fat thickness in healthy volunteers to the body fat (8). The body weight minus the estimated total body fat was called the lean body mass. In an attempt to estimate the amount of water in the lean body mass, the total body water was measured in 10 of the patients by determining tritium activity in serum 24 hours after oral administration of 100  $\mu\text{Ci}$  of  $^3\text{H}_2\text{O}$  with correction for excreted tritium activity. The difference between the lean



Table I Description of the patients

AML=acute myeloid leukemia APL=acute promyelocytic leukemia ALL=acute lymphatic leukaemia  
AMML=acute myelomonocytic leukemia n s =not studied

Pat no	Age (y)	Sex	Weight (kg)	Diagnosis	Duration of complete and partial remission (mo)	Duration of disease (mo)	Notes
1	61	♀	n s	AML	—	1	—
2	32	♀	64.6	AML	—	6	—
3	59	♂	69.7	AML	8	12	—
4*	65	♀	51.5	AML	10	15	Adynamia terminal diabetes mellitus
5*	56	♀	76.0	AML	16	23	Adynamia psychosis
6*	36	♀	80.0	AML	22	24	Arrhythmia
7	33	♂	70.2	ALL	19	23	—
8	67	♀	57.0	APML	2	6	Arrhythmia
9	43	♂	52.1	APML	4	10	Adynamia
10	40	♀	50.2	AML	2	10	Muscular pains
11	54	♂	n s	AML	—	1	Arrhythmia
12	56	♂	88.0	AMML	7	10	Hypertonia alcoholism
13	27	♂	62.5	AML	11	16	Increased intracranial pressure
14	49	♂	74.6	AML	7	10	Acromegaly hypophysectomy
15	33	♀	n s	di Guglielmo	—	3	Preleukemia for 1 y
16	65	♀	59.1	AML	6	14	Tuberculoma heart failure
17	53	♀	53.0	APML	6	11	Diabetes insipidus
18	71	♀	62.2	AML	7	13	Arrhythmia
19*	53	♀	85.6	AML	10	20	Adynamia seizures
20	80	♀	n s	AL	—	1	<sup>32</sup> P treated PCV in 1969
21	45	♂	80.0	AMML	—	6	Arrhythmia
22	55	♂	69.1	APML	7	11	Diabetes insipidus arrhythmia

\* Not studied in the initial phase of the disease

v mass and the total body water was called the dry body mass

**Total body potassium concentrations:** The total body potassium was expressed per kg of body weight and of the body compartments lean body mass dry lean body mass and total body water. To facilitate the statistical analysis all individual values were expressed as per cent of the mean control value for the corresponding age and sex group

**Serum and urinary electrolytes and isozymes** Serum

and urinary potassium and sodium concentrations determined by Technicon Flame Photometry at the Central Laboratory. The normal ranges for potassium in this laboratory are 3.5–4.9 mmol/l in serum and 3 mmol in 24-hour urine and for sodium 137–145 mmol/l serum. Arbitrarily in order to estimate the frequency of hypokalemia conservatively borderline hypokalemia not called hypokalemia and only potassium values  $< 3.2$  mmol/l serum were considered as evidence of hypokalemia. Serum concentrations of zinc, mag-

Table II Potassium concentration in different body compartments in controls (mean  $\pm$  S.D.)

		Potassium concentration (mmol/kg)			
	No of subj	Per body weight	Per lean body weight	Per dry lean body mass	Per total body water
<i>Males</i>					
Under 50 y	25	51.4± 5.9	64.2±5.4	276.2±60.6	86.2± 9.2
Over 50 y	21	38.9±10.0	63.2±7.7	273.7±57.5	80.6±11.8
<i>Females</i>					
Under 50 y	29	43.7± 5.4	56.2±6.9	237.9±42.5	77.2±10.2
Over 50 y	13	36.3±9.0	52.7±6.6	212.3±33.0	74.4± 6.1

le III Int l eas re e t of total p t ss ias percent fcorrespo d a control nean

	k/kg body we ght	k/kg lean body mass	K/kg dry lean body mass	k/kg total body water
	87	86	56	100
	88	80	106	76
	80	74		
	80	88		
	98	111	83	118
	110	103		
	104	130		
	10	96		
	70	72	55	76
	78	74	87	73
	95	81	97	76
	71	73	59	76
	96	111		
	64	58	67	54
	8	111		
	64	78		
	77	77	61	79
	86	68	70	70
	84.8	87.3	77.6	79.8
	+13.5	+19.0	+17.4	+17.4
of pats	18	18	10	10

alc um were measured by atom c absorpt on meas  
ents w th the Perk n Elmer 303 and 403 apparatus  
ct ely The normal ranges of the laboratory are

5  $\mu\text{mol/l}$  0.72-0.90 mmol/l  $\gamma$  20-2.60 mmol/l respec

Lysozyme in serum and urine was measured by a  
metric method (26) reported to g ve normal values of

5 mg/100 ml in serum and under 0.2 mg/100 ml

me In a few cases lysozyme was measured by a cup  
method (16) giv ng normal values of 4-14  $\mu\text{g}$  hen

h te lysozyme (HEWL)/m n serum and of 0-0.7  $\mu\text{g}$

L/ml n urine Normal range for serum album n s

g/l

rmone assa s Urinary excret ons of aldosterone and

fre n concentra ons of ren n were de erm ned n 13 of

o ems by the Endocrinology Laboratory Ren n was

m ned n fast ng pa ents n the morn ng by a New

and Nuclear Rad o mmune Assay k t Aldosterone

determ ned by a rad o mmune assay method (34)

nal values for ren n act v ty were 0.5-1.5 ng/ml/hour

e p one pos on Normal urinary aldosterone excre

was 5-17  $\mu\text{g}/24$  hours The values were nterpreted n

on o urinary exc et on of sod um and potass um

potass um per kg body weight per kg lean body

mass per kg dry lean body mass and per kg water

The relat ve potass um def c t per kg dry lean body

mass in the whole group was 77% of the control

value Eleven of the 18 pat ents stud ed had de

creased potassium per kg lean body mass on one

occas on Individual potass um def c t was found in

6 of 18 patients in whom the potassium per kg lean

body mass was under the 95% confidence l mit of

the controls Th s frequency is h ghly sign f cant

( $p < 0.001$ ) Repeated measurements were per

formed in 14 pat ents 5 of whom showed a s gnifi

cant change in their total body potassium concentra

tion—7 from a normal to a low and 3 from a low to a

normal value One patient (no 8) had a statist cally

s gn f cant ncrease in potass um per kg lean body

mass

## RESULTS

### l bod potass

results from the total body potass um meas

urents are g ven in Table II for the controls and

able III for the leukemia pat ents The mean

entrat on was s gnif cantly lower in the pat ents

in the controls ( $p < 0.001$ ) Th s was true for

### Ser n electrol tes

Twelve of the 27 pat ents had interm ittent hy

pokalem a Two of these 17 pat ents had less than

3.0 mmol/l for over 3 weeks 6 of the pat ents had

hypokalem a on adm ssion before any treatment

had been given Serum magnes um was decreased

interm ittently in 8 of 70 pat ents serum calc um n

15 of 20 serum zinc n 13 of 17 and serum sod um n

13 of 21 Two patients had hypermagnesem a Al

kalos s was found interm ittently n 9 of the 77 pa

Table IV Total body potassium in relation to stage of disease (A) treatment and hypokalemia (B)

Potassium per kg lean body mass	Relapse	Complete and partial remission
<b>A Samples (n=39)</b>		
Normal (n=20)	12 (60%)	8 (40%)
Increased (n=1)	1	
Decreased (n=18)	13 (72%)	5 (28%)
	Cytostatic courses until 1st measurement (Mean and range)	Hypokalemia
<b>B Patients (n=18)</b>		
Normal (n=6)	4 (0-15)	3 (50%)
Increased (n=1)	2	
Decreased (n=11)	5 (0-16)	7 (64%)

tients. The individual means for serum albumin in 21/22 patients ranged between 25 and 41 g/l.

#### Hormone assays and urinary electrolytes

Aldosterone in urine and/or renin in plasma was increased in 8 of 13 patients. Increased values varied between 5.0 and 12.1 ng/ml/hour for renin and between 8.4 and 57.8 µg/24-hour urine for aldosterone. Five of the 8 patients had hypokalemia while 3 had normal serum potassium. Despite increased serum aldosterone or renin in 7 patients with hypokalemia, no hormone assays were available. The urinary Na/K ratio was pathological (<1.0) in 7/12 hypokalemic and 3/10 normokalemic patients while the mean urinary potassium excretion was normal in the normokalemic patients. The individual mean value exceeded 57 mmol/24 hours for each hypokalemic patient. Four of the patients had mean values exceeding 100 mmol/24 hours despite hypokalemia.

#### Lysozyme

The lysozyme values were increased in 13 of 21 patients. Of the 13 patients with high values, 8 had decreased serum potassium. Four patients had normal lysozyme values despite a low serum potassium.

#### Relations between whole body potassium and other clinical data

Table IV presents some relations between clinical data and potassium per kg lean body mass. Among the 11 patients with decreased total body potas-

sium, 7 had intermittent hypokalemia but only these had hypokalemia at the time of the measurement.

However, when all whole body potassium measurements were taken into account, there was no statistical difference either between the whole body potassium in relapse and remission or between the first and the last measurement. Neither could a correlation be found in the whole group between the percentage of blasts or the WBC in the peripheral blood and the total body potassium. The amount of cytostatics given was not higher in the potassium-depleted patients than in those with a normal potassium per kg lean body mass (Table IV). For patients not studied in the initial phase of disease, 7 of 10 measurements while the corresponding figure for the others was 12 out of 29 measurements.

## DISCUSSION

The various methods for estimating lean body mass have been compared recently (13). The anthropometric techniques for estimating lean body mass, the skinfold technique and the more exact determination of the total body water, yielded comparable results for controls and patients. According to Delwaide (12), the clinical estimation of total body potassium is limited by its wide range and therefore it is preferable to compare groups of patients rather than individuals.

Considerable problems in evaluation of whole body potassium values are the errors of measurements and the biological variations. The most difficult problem is that of comparing potassium per lean body mass in patients with that in controls. The significantly decreased total body potassium values might be due to a changed body composition. The comparison becomes invalid if for instance differences in the hydration of the lean body exist. However, the results of total body water balance studies show comparable figures in the patients and controls. Moreover, the body weights of the patients were within normal range.

Some of our patients had a previous history of diseases possibly associated with disturbed potassium metabolism (Table I), such as hypothyroidism, acromegaly (1) and alcohol abuse. However, some recent reports claim that there is no significant decrease in total body potassium in patients on diuretic therapy of hypertension (37) and some

as even maintain that potassium supplementation is unnecessary (11). Similarly, no cirrhosis of liver was revealed at autopsy in the patient with alcoholic abuse and potassium depletion without jaundice. This is not reported in alcoholics. For these reasons and because it was considered valuable to study a consecutive series of patients, these patients were included in the study. The only ones excluded (from total potassium measurement) were patients aged 1 and 20 who either died prematurely and patient 15 who had been given isotopes making the potassium study impossible.

Compared with the controls, the patients had a significantly lower value of potassium per kg lean body mass. Thus hypokalemia which has been demonstrated in acute leukemia (17) is accompanied by a decrease in the total body potassium. But the present results confirm the findings of other reports that there is no simple relationship between the body and serum potassium (7).

Some of our patients showed a significant increase in total body potassium, thus suggesting that potassium depletion is reversible, a finding that confirms similar findings by Delwaide (12). The factors responsible for hypokalemia and potassium retention in leukemia cannot yet be completely clarified. Our data suggest a potassium loss in the majority of patients with a low potassium value per unit body mass. The single case with increased total body potassium could, like a previous case, be explained by the hypothesis that there is an intracellular redistribution of potassium in leukemia which accounts for the hypokalemia (24) and a subsequent increase of the total potassium due to reabsorption efficiency following the redistribution. Further studies are in progress to elucidate the latter problem.

Several authors have reported altered cell membrane potentials and increased intracellular levels of potassium both in patients with potassium depletion and with malignant disease and uremia (4, 6, 10).

Leit (36) introduced the concept 'sick cell syndrome' to integrate the different findings in cells in severely ill patients. He found high intracellular levels of sodium in erythrocytes of patients with malignant disease. By studying the ouabain sensitive part of the cell membrane pump, he found a defect which could explain the phenomenon. Mir et al (22) confirmed this finding interestingly in leukemic subjects. In addition they found evidence

for a serum factor in acute leukemia which influenced the activity of the ouabain sensitive pump. The 'sick cell' concept might be generalized to other cells in the body besides the erythrocytes on which the original studies were made (36). Besides the membrane function of potassium, its metabolic aspect must also be considered. Scribner and Burnell (33) using the concept 'potassium capacity' emphasized the metabolic role of potassium in the cells. Further studies are necessary to see whether these theories are applicable to leukemic patients.

The results show that there are other electrolyte disturbances besides hypokalemia in leukemia as reported by others (14, 17, 21, 39, 40). Vincristine and cyclophosphamide are known to influence the sodium levels in serum (9, 21) but hyponatremia without known cause is also reported in leukemia (25). Magnesium is affected by secondary hyperaldosteronism which was found in some of the patients and there is a relationship between magnesium depletion and hypokalemia (30). In the investigation of this spectrum of electrolyte disturbances, the possibility of multiple primary tumors which might be endocrine must be considered at least in lymphatic malignancies (20). Also leukemic infiltration or coagulation disorders might damage endocrine organs such as the pituitary (3, 32).

Ecotopic hormone production (28, 39) in malignancy and leukemia must be discriminated from multiple primary tumors with endocrine activity (20). In a situation where the remission frequency in leukemia is improving (15) and where progress is being made in fighting septicemia and bleeding, the traditional causes of death in leukemia, decreased whole body potassium and electrolyte disturbances may become clinically relevant.

#### ACKNOWLEDGEMENTS

Supported by Swedish Cancer Society; grant no. 4158 and Swedish Medical Research Council; grant no. B 74-19X-4158 038.

#### REFERENCES

1. Alcié J F, Roginsky M S, Jowsey J, Dombrowski C S, Shukla K K & Cohn S. Skeletal metabolism and body composition in acromegaly. *J Clin Endocrinol Metab* 35: 543, 1972.
2. Appel G B & Neu H C. The nephrotoxicity of antimicrobial agents. *N Engl J Med* 296: 663, 1977.
3. Bergman G E, Baluarte H J & Naiman J L.

- Diabetes insipidus as a presaging manifestation of acute myelogenous leukemia. *J Pediatr* 88: 355 1976
- Bohte H. D., Decker E. & Voller W. Changes of ionic permeability of skeletal and heart muscle cellular membranes in renal insufficiency. In: *Uremia* (ed. R. Nijhe, G. Berline & B. Burton) p. 14. Thieme Verlag, Stuttgart 1972.
- Bohte H. D. & Ludertitz, B. Chronischer Kaliummangel und muskellucluläre Erregbarkeit. *Klin Wochenschr* 1: 34 1970
- Campion D. S., Carter N. W., Rector F. C. & Seldin D. W. Intracellular pH in chronic potassium deficiency in the rat. *Clin Res* 16: 379 1968
- Carlmark B., Krombout, D. & Reizenstein P. Total body potassium measurements in 230 patients. *Scand J Clin Lab Invest* 35: 617 1975
- Carlmark, B. & Reizenstein, P. Human body composition studies. Neutron activation of total body hydrogen and whole-body counting. "In vivo neutron activation analysis." IAEA panel Vienna 1972.
- Chabner B. A., Myers C. E., Coleman, C. N. & Johns D. G. The clinical pharmacology of antineoplastic agents. *N Engl J Med* 29: 1166 1975
- Cunningham, J. N., Carter N. W., Rector F. C. & Seldin, D. W. Resting transmembrane potential difference of skeletal muscle in normal subjects and severe ill patients. *J Clin Invest* 50: 49 1971
- Darge H. J., Boddy K., Kennedy A. C., King, C. K., Read, P. R. & Ward, D. M. Total body potassium in long-term furosemide therapy: is potassium supplementation necessary? *Br Med J* 4: 316 1974
- Delwaide P. H. Body potassium measurements by whole body counting scanning of patient populations. *J Nucl Med* 14: 40 1973
- Delwaide P. H. & Crentier E. J. Body potassium as related to lean body mass measured by total water determination and by anthropometric method. *Hum Biol* 45: 599 1973
- Fredricks R. E., Tanaka, K. R. & Valentine W. N. Variations of human blood cell zinc in disease. *J Clin Invest* 3: 304 1964
- Gale R. P. & Cline M. J. High remission-induction rate in acute myeloid leukemia. *Lancet* 1: 497 1977
- Harrison J. F. & Barnett A. D. The urinary excretion of lysozyme in dogs. *Clin Sci* 38: 1533 1970
- Hocker P. & Reizenstein P. Calcium and potassium disturbances in acute leukemia. *Blut* 29: 398 1974
- Kritzer R. A. Anuria complicating the treatment of leukemia. *Am J Med* 25: 532, 1958
- Lantz B. Electrolyte disturbances in acute leukemia. Frequency and possible mechanisms. *Int. Soc. Haematol. 3rd meeting*. London (Abstr.) 21-43 1975
- Lantz B., Adolfsson J., Lagerlof B. & Reizenstein P.. Multiple primary tumours in lymphoma. To be published.
- Mertwether D. W. Vincristine toxicity with hyponatremia and hypochloremia in an adult. *Oncology* 25: 234 1971
- Mir M. A. & Bobinski H. Altered membrane sodium transport and the presence of a plasma ouabain-like inhibitory factor in acute myeloid leukemia. *Clin Sci Mol Med* 48: 213 1975
- Mir M. A., Brabin B., Tang, O. T., Leslee & Delamore I. W. Hypokalemia in acute leukemia. *Ann Intern Med* 82: 54 1975
- (Letter). *Ann Intern Med* 83: 855 1975
- Mir M. A. & Delamore I. W. Hyponatremia in AML. *Br Med J* 1: 52 1975
- Modeer T. & Soder P.-O.. A diffusion method for determination of lysozyme activity. *Scand J Clin Lab Invest* 79: 533 1971
- Muggia F. M., Heinemann N. O., Farag, Osseman E. F. Lysozymuria and renal dysfunction in monocytic and leukemia. *Am J Med* 47: 351 1969
- Orianni P. G. S. Pathobiology of ectopic production by neoplasms in man. *Pathol. Ann.* 1971
- Parker A. C., Lambie A. T., Housley E. & son J. Plasma potassium levels in leukemia. *J Clin Pathol* 30: 1392 1975
- Reddy C. R., Coburn J. W., Hartenbowel I., Friedler R. M., Bruckman A. S., Massry S., Jowsey J. Studies on mechanisms of hypomagnesemia in chronic renal failure. *J Clin Invest* 52: 300 1973
- Reizenstein P. & Karlsson H. A. Clinical body counting. Whole body scanning with isotopes. *Acta Radiol* 4: 209 1966
- Rosenzweig A. J. & Kendal J. W. Diabetes insipidus as a complication of acute leukemia. *Intern Med* 117: 397 1966
- Scribner B. H. & Burnell J. M.. Serum potassium concentration. *Metabolism* 19: 1946
- Sealy J. E. Aldosterone excretion. Physiological variations in man measured by radioimmunoassay with double isotope dilution. *Circ Res* 31: 367 1972
- Uden A. M., Brenning G., Engstedt, L. F., S. Gahrton G., Gullbring B., Holm, G. H., S. Jameson S., Killander A., Killander D., ner D., Mellstedt H., Palmblad J., Skarberg K.-O., Swedberg B., Wadman B. & L. L. L-asparaginase and prednisolone treatment followed by rubidomycin and cytosine arabinoside induction of remission in adult patients with myeloblastic leukaemia. *Scand J Haematol* 1975
- Welt, L. G. Membrane transport defect, the uremic syndrome. *Trans Assoc Am Physicians* 77: 217 1967
- Wilkinson P. R., Hesp R., Issler H. & Raz B. Total body and serum potassium during furosemide therapy for essential hypertension. *J Clin Pathol* 1: 759 1975
- Young, G., Sullivan, J. & Burley T. Hypokalemia due to gentamycin/cephalosporin in leukemia. *Am J Med* 1: 2: 855 1973
- Zidar B. L., Shaduck R. K., Winkler, Ziegler Z. & Hawker C. D. Acute myeloid leukemia and hypercalcemia. *N Engl J Med* 294: 1976
- Zusman J., Brown D. M. & Nesher R. Hyperphosphatemia and hypocalcemia in lymphoblastic leukemia. *N Engl J Med* 299: 1973

## Self-Poisoning Treated in the ICU

Andrew Heath and Dag Selander

From the Department of Anaesthesiology and Intensive Care, Sahlgren's Hospital, Gothenburg, Sweden

**TRACT** This retrospective study compares the number and type of self poisonings admitted to the intensive care units (ICU) at Sahlgren's Hospital, Gothenburg, during 1972 and 1976. The total number of patients requiring intensive care was unchanged, but a change in the pattern of self poisoning was seen. In 1976 the number of patients requiring intensive care following acute alcohol intoxication increased, whereas the number of barbiturate and methaqualone poisonings decreased. Tricyclic antidepressants formed the largest group in both years. Fewer patients needed endotracheal intubation or IPPV in 1976 than in 1972. Also, fewer complications were seen and the death rate among ICU-treated patients decreased. In the Gothenburg area, barbiturates accounted for one half of all deaths due to self poisoning and tricyclic antidepressants for one third. Any expected decrease in intensive care as a result of fewer barbiturate and methaqualone poisonings was obscured by an increase in severe alcohol intoxication.

**Keywords:** self poisoning, intensive care, drug pattern, mortality.  
Acta Med Scand 206: 51-54, 1979.

Many cases of self poisoning admitted to hospital intensive care. The object of this paper is to report the results of a retrospective study involving self poisoning treated in the intensive care units at Sahlgren's Hospital, Gothenburg, during the years 1972 and 1976. The number of patients admitted, drugs used and the time and type of treatment in the ICU are evaluated.

## METHODS

The total number of cases of self poisoning with drugs, with or without alcohol or with alcohol alone, was determined from the admission lists of the Emergency and Accident Department for the years 1972 and 1976. Data concerning patients cared for in the ICUs were taken from the ICU records. Figures concerning the number of deaths in 1972 and 1976 in Gothenburg as a result of self poisoning were taken from the records of the National Forensic Laboratory, Gothenburg.

Principles for ICU treatment were in agreement with the so-called Scandinavian model (5, 11, 12): gastrointestinal lavage, close observation, assisted ventilation and forced diuresis when indicated.

Drugs were classified into one of the following groups: barbiturate, methaqualone, other hypnotic, anxiolytic, analgesic, tricyclic antidepressant, alcohol only or other. The other group included other drugs and non medicinal agents. Cases of polydrug overdosage were placed into one group only where barbiturates took precedence thereafter tricyclic antidepressant, methaqualone, other hypnotic drugs and anxiolytic drugs in this order respectively. Consequently all cases of barbiturate poisoning are shown in the figures presented, but the group anxiolytic drugs, in which the benzodiazepine and phenothiazines are included, is underrepresented. However the barbiturate and tricyclic groups are comparable since there was only one case where a barbiturate and a tricyclic antidepressant were known to have been taken together. Although the barbiturate and anxiolytic groups may not directly be compared with each other, we assumed that changes within these groups from 1972 to 1976 are reflected.

## RESULTS

## Hospital admissions

The total number of hospital admissions due to deliberate self poisoning is shown in Table 1. Of the patients admitted, 362 (15.2%) were transferred to an ICU in 1972 and 339 (11.2%) in 1976. Of patients admitted in 1972, 179 were men and 183 women; in 1976, 168 were men and 171 women. Three quarters of these patients were under the age of 40 and in both sexes there was a peak incidence in the 20s. In 1976 cases of self poisoning accounted for 14.8% of patients requiring intensive care.

The distribution of ingested drugs is illustrated in Fig. 1. There was a considerable reduction in the proportion of self poisonings due to barbiturates and methaqualone, whereas poisonings due to tricyclic antidepressants and anxiolytic drugs were equal in 1972 and 1976.

Address for reprints: Dr A. Heath, Department of Anaesthesiology and Intensive Care, Sahlgren's, S-41345 Gothenburg, Sweden.

Table I Patients admitted to the Emergency and Accident Department because of self poisoning  
 Figures in parentheses indicate patients admitted to ICU

1972				1976			
2 379 (362)				2 925 (339)			
Self poisoning with/ without alcohol		Alcohol only		Self poisoning with/ without alcohol		Alcohol only	
1 516		863		1 793		1 132	
♂	♀	♂	♀	♂	♀	♂	♀
787	729	759	104	805	988	962	170

The number of patients cared for in the ICU because of alcohol intoxication only rose from 18 (5%) in 1972 to 47 (13.9%) in 1976. Likewise the number of patients taking alcohol together with a drug rose from 70 (19.3%) in 1972 to 97 (28.6%) in 1976. Polydrug overdosage occurred in 186 (51.4%) of patients in 1972 and 172 (50.7%) in 1976.

In the barbiturate group there was an equal distribution between the sexes in both years studied whereas females strongly predominated in the tricyclic antidepressant group.

Observation times are given in Table II. Fewer patients needed intubating in 1976 than in 1972 and likewise fewer patients required assisted ventilation.

However, of those requiring assisted ventilation the time spent on the ventilator was about the same in 1972 and 1976.

Aspiration occurred in 7.7% of patients and 3.2% in 1976, usually before arrival at hospital. Pressure necrosis was seen in a few patients. Malignant cardiac arrhythmias in self poisoning with tricyclic antidepressants are rare.

### Deaths

In 1972, 10 patients (2.8%) and in 1976, 1 (1.2%) admitted to an ICU died of self poisoning. The drugs taken are listed in Table III.

In the Gothenburg area a total of 70 deaths from self poisoning were registered in 1972 and 1976. Barbiturates accounted for almost half the deaths in both years and tricyclic antidepressants for about a fifth (Table IV). A commonly used analgesic and sedative preparation containing salicylic acid, dextropropoxyphene and aspirin accounted for 13 deaths (18.6%) in 1972 and 9 deaths (15.8%) in 1976.

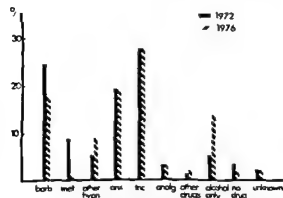


Fig. 1 Self poisonings admitted to ICU expressed as % of total admissions in 1972 and 1976. Barb = barbiturate, met = methaqualone, other hypn = other hypnotic, tric = tricyclic antidepressant, anx = anxiolytic, analg = analgesic. No drug includes poisonings from non medicinal agents.

Table II Observation times, intubation and assisted ventilation in the ICU

	1972
Mean observation time (h)	
All patients	30.0
Barbiturate group	43.0
Tricyclic antidepressant group	24.1
Patients requiring endotracheal intubation (%)	46.1
Patients requiring assisted ventilation (%)	18.5
Mean assisted ventilation time (h)	29.5





The decrease in deaths among ICU-treated self poisonings seemed at least in part to be due to a decrease in barbiturate poisonings. However, almost one half of fatal self poisonings in the Gothenburg area were in both years caused by barbiturates. A similar proportion was recently reported by Johns (7) from England and Wales. Despite a reduction of the number of hospital admissions due to barbiturate poisoning and of barbiturate prescriptions, Johns found no corresponding reduction in the number of deaths. The tricyclic antidepressants remain next to the barbiturates the largest group responsible for deaths by drug overdosage in the Gothenburg area, almost a fifth of the total number of deaths.

A large number of deaths were caused by self poisoning with a combination of aspirin, dextropropoxyphene and barbiturate. In Gothenburg, this combination alone accounted for as many deaths as the tricyclic antidepressants. This finding confirms earlier reports of the high toxicity of dextropropoxyphene, especially in combination with alcohol (4, 16, 17) or barbiturates.

### CONCLUSIONS

Our study suggests that a reduction in barbiturate prescription results in fewer patients requiring intubation and assisted ventilation and fewer complications, a consequent reduction of intensive care costs. However, any such reduction was offset by an increase in the number of alcohol intoxications requiring intensive care. Also, we hope that pointing out the danger of a combination of dextropropoxyphene with a barbiturate or alcohol will decrease the prescription of dextropropoxyphene.

### REFERENCES

- 1 Afzelius-Frisk J & Gustavsson Å. *Toxikationer i Göteborg under 1962*. Lakartidn 60:3325 1963
- 2 Bean P. Patterns of self poisoning. *Br J Hosp Med* 28:24 1974
- 3 Berg K J. *Forgifning med psykoterapeutiske Fremskrift* 3:117 1969
- 4 Carson D J L & Carson E D. *Propoxyphene poisoning*. *Br Med J* 2:105 1976
- 5 Clemmensen C. *New line of treatment in barbiturate poisoning*. *Acta Med Scand* 148:83 1954
- 6 Ghodse H H. *Deliberate self poisoning: A study of London casualty departments*. *Br Med J* 1:184 1974
- 7 Johns M W. *Self-poisoning with drugs in England and Wales during 1959-1974*. *Br Med J* 1:128 1977
- 8 Kessel N, McCulloch M & Simpson E. *Barbiturate treatment in a centre for the poisoning*. *Br Med J* 985 1963
- 9 Kreitman N. *Aspects of epidemiology of "attempted suicide" (parasuicide)*. In *Attempted suicide* (ed J Waldenström) p 45. Bokhandelns Förlag, Stockholm 1972
- 10 Matell G. *Somatic aspects in suicidal suicide* (ed J Waldenström) p 281. Bokhandelns Förlag, Stockholm 1972
- 11 Michetzyk A & Lassen N A. *Urea molic diuresis and alkalization of urine in barbiturate intoxication*. *JAMA* 185:936 1963
- 12 Nilsson E. *Treatment of acute barbiturate poisoning*. *Acta Med Scand* (Suppl) 253:1951
- 13 Proudfoot A T & Park J. *Changing drugs used for self poisoning*. *Br Med J* 1:90 1971
- 14 Ross F J. *The management of the pre-suicidal and post-suicidal patient*. (UCLA Ann Intern Med 75:441 1971)
- 15 Smith A J. *Self poisoning with drugs: A situation*. *Br Med J* 4:157 1972
- 16 Tennant F S. *Complications of propoxyphene abuse*. *Arch Intern Med* 132:191 1973
- 17 Whittington R M. *Dextropropoxyphene (Talwin) overdosage at the West Midlands*. *Br Med J* 2:172 1977

# Emergency Room Resuscitation of Patients with Cardiac Arrest outside Hospital

## *Outcome and Immediate Prognosis in 319 Patients*

Leif R. Erhardt, Magnus Sederholm and Ingrid Gertz

*From the Departments of Medicine and Anaesthesiology  
Serafimerlasarettet, Stockholm, Sweden*

**Abstract** Resuscitation was attempted in 319 patients brought to hospital with cardiac arrest during a 5-year period. Primary successful results were achieved in 50 patients (15.7%). Twelve patients were short-term survivors (3.4%), 10 of whom had normal brain function, whereas 2 had mild cerebral dysfunction. To improve prognostication in patients with initially successful resuscitation, Bayes' theorem was used using 4 clinical findings after 24 hours: mentation reactions to painful stimuli, pupillary size, reflex reactions and BP. Bayes' theorem as well as a depth after 24 hours gave valuable information during individual prognosis.

**Keywords:** cardiac arrest, resuscitation, prognosis, Bayes' theorem.

Acta Med Scand 206: 55, 1979.

Recognition of cardiac arrest occurring outside hospitals has proved difficult. Attempts have been made to increase survival by the use of specialized ambulances which rapidly can assist the patient at the site of the accident (1, 8, 14, 17). However, in many places such ambulance systems are not available and patients with cardiac arrest are brought to hospital by ordinary ambulances for resuscitation. Due to the long delay before resumption of the circulation under these circumstances, chances of survival are usually poor (9, 10). We have studied the results of resuscitation in an emergency room of patients with cardiac arrest occurring outside hospital during a five year period. Resuscitation of patients with long standing arrest will often lead to permanent brain damage in the absence of adequate circulation. Early prognostication in these cases would be of great value. Therefore we also attempted to find parameters of prognostic value to improve clinical decision making.

## PATIENTS AND METHODS

During the period July 1, 1972-June 30, 1977 resuscitation was attempted in 319 patients in the emergency room at Serafimerlasarettet in Stockholm. Resuscitation was started when the preliminary history indicated that the time of arrest had been short, i.e. approximately less than 15 min. Before, during and after the resuscitation notes were made on parameters such as cardiac rhythm, neurological status, breathing pattern, blood pressure (BP), etc. Patients who after the resuscitation had palpable pulse, BP and adequate peripheral circulation were taken to the intensive care unit (ICU) for respirator treatment. All patients received cortisone and were hyperventilated to reduce cerebral oedema.

Bayes' theorem was used to calculate the probability of fatal outcome on the basis of available clinical and laboratory data during the first 24 hours. The probability of a given patient having a certain outcome can be estimated by this theorem, which in the medical context enables the known frequency of indicants (information from history, clinical features and special investigations) in a disease to be used for diagnostic calculations.  $\chi^2$  test with Yates' correction was used for comparing differences between patient groups.

## RESULTS

Resuscitation was unsuccessful in 269 (84%) of the 319 patients and these patients were not further studied. In 50 patients (15 women and 35 men) stable circulation was achieved and they were transferred to the ICU. Altogether 38 hospital deaths occurred among these 50 patients: 16 in the ICU and 22 in general medical wards (short-term survivors). Eleven patients were discharged alive from hospital (long-term survivors). One additional

**Abbreviations:** ICU=intensive care unit, CCU=coronary care unit, VF=ventricular fibrillation, BP=blood pressure.

Table I ECG pupillary size and pupillary reaction to light on admission in 50 resuscitated patients

	Grade of pupillary dilatation			Pupillary reaction to light			Initial ECG	
	Max	Normal	Unknown	Pos	Neg	Unknown	VF	Asy agonal
Long term survivors (n=12)	5	4	3	5	5	2	10	2
Short term survivors (n=38)	28	10	0	5	30	3	15	23
Significance of difference	N S			N S			p<0.05	

patient who was mobilized without residual cerebral dysfunction but died of reinfarction two days before planned discharge is also included among the long term survivors. There was no difference in age between long and short term survivors ( $67.0 \pm 11.8$  and  $67.6 \pm 7.5$  years respectively). Thus 3.4% of the 319 patients admitted with cardiac arrest survived to leave hospital. Among the long term survivors 10 were without any intellectual impairment while two had mild cerebral dysfunction.

#### Time factors

Estimations of the interval between onset of cardiac arrest and the beginning of cardiopulmonary resuscitation outside hospital were available for 8 of the 12 long term survivors and for 26 of the 38 short term survivors. The mean interval in the latter group was  $6 \pm 4$  min and  $2 \pm 2$  min in the former ( $p < 0.05$ ). In contrast there was no difference between long and short term survivors as regards the

interval between onset of cardiac arrest and admission to hospital. Three long term survivors had very long delays (20, 28 and 45 min respectively) but in all these cases medically trained persons were near by and immediately started cardiopulmonary resuscitation and artificial ventilation (Fig. 1).

#### Hospital course of primary successful resuscitations

Pupillary light reactions and size on admission did not differ among long and short term survivors (Table I). Three of the long term survivors had fixed dilated pupils. Ten long term and 19 short term survivors had ventricular fibrillation on admission ( $p < 0.05$ ). Ten of 25 patients with asystole or agonal rhythms could later be discharged (N.S.). There was no difference in assessed time of circulatory arrest between patients with VF or asystole on admission. Spontaneous respiration recurred significantly more often among long term than short term survivors immediately after successful resuscitation ( $p < 0.05$ ). Hypotension (BP < 90 mmHg) during resuscitation was seen in 10 patients, but after successful resuscitation was restored in 9 patients (Table II). Twenty four hours after successful resuscitation all long term survivors had normal pupillary reactions, normal response to painful stimuli and normal BP. None of the long term survivors still in coma after 24 hours could be discharged, while 12 of 13 non-comatose patients were discharged as long term survivors (Table III). The diagnoses are listed in Table IV. In the majority of the patients the underlying cause of cardiac arrest was myocardial infarction. An unsuspected high frequency of cerebrovascular lesions (7/30) was found in the autopsied cases.

#### Prognostic model

The probability of a fatal outcome in all resuscitated patients (prior probability) was  $38/50$  i.e. 0.76.

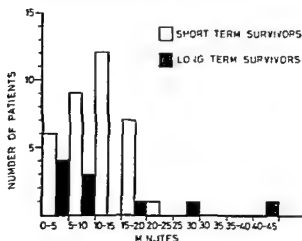


Fig. 1 Interval between onset of cardiac arrest and arrival at the emergency room in 50 successfully resuscitated patients. Note that two long term survivors have a very long delay.

Table II Pupillary size and light reaction BP and breathing pattern immediately following resuscitation in relation to survival

	Grade of pupillary reaction			Pupillary light reaction			Systolic BP (mmHg)			Spontaneous breathing		
	Max	Nor mal	Un known	Pos	Neg	Un known	>90	<90	Un known	Pres ent	Ab- sent	Un known
Long term survivors (12)	1	11	0	9	2	1	11	0	1	10	2	0
Short term survivors (38)	8	28	2	21	12	5	24	11	3	14	23	1
Significance difference	N S			N S			N S			$p < 0.05$		

Resuscitation was repeated for new indicants and a conditioned probability was constructed. The probability of survival/fatal outcome was calculated from four items of information (indicants)—reaction to painful stimuli, pupillary light reaction and BP 24 hours after resuscitation. These indicants were chosen because they appeared to have predictive power. *Example* A patient has the following physical signs 24 hours after resuscitation: normotensive, fixed dilated pupils and no reaction to painful stimuli. The probability of fatal outcome derived from Bayes' theorem is 0.999. Another patient is normotensive (BP > 90 mmHg), has normal pupillary light reaction and size and adequate response to painful stimuli. The probability of fatal outcome is 0.27, i.e. the likelihood of survival is 0.73.

## DISCUSSION

Our reports regarding resuscitation in emergency rooms have been published while experience of

resuscitation of patients already admitted to hospital and in mobile coronary care units (CCU) is well documented (1, 8, 14, 17, 18). In one series from Oslo, four (5%) of 76 patients resuscitated in an emergency room after cardiac arrest outside hospital could be discharged (9). Seven (8%) of 84 admitted patients could be discharged in another series from Copenhagen (10). In that study nearly 50% of the patients had asystole on admission and none of these survived to leave the hospital. The results from our study as well as those from CCUs or mobile CCUs are in agreement with these findings (10, 13, 17). Patients with VF may be thought to have a shorter delay prior to resuscitation, but we did not find any significant trend to support this supposition. The difference in prognosis between patients with asystole and VF may also have an additional explanation. VF may occur without major myocardial damage, as distinguished from asystole which more commonly may be secondary to extensive septal damage with resultant complete heart

Table III Pupillary size and light reaction, pain reaction and BP in relation to survival 24 hours after resuscitation

	Grade of pupillary dilatation			Pupillary light reaction			Systolic BP (mmHg)			Reaction to painful stimuli		
	Max	Nor mal	Un known	Pos	Neg	Un known	>90	<90	Un known	Pos	Neg	Un known
Long term survivors (12)	0	12	0	12	0	0	12	0	0	12	0	0
Short term survivors (38)	8	26	4	14	20	4	25	8	5	11	20	7
Significance difference	N S			$p < 0.01$			N S			$p < 0.001$		

Table IV Diagnoses in 50 resuscitated patients

Short term survivors* (n=38)		Long term survivors (n=12)	
Myocardial infarction		Myocardial infarction	
Recent	6	Recent	2
Old	2	Suspected	5
Recent and old	14	Primary VF	4
Stroke	3	Drowning	1
Subarachnoidal bleeding	4		
Pulmonary embolus	1		
Unknown	8		

\* 30 patients autopsied

block. Furthermore, the VF may have been preceded by ventricular tachycardia giving some but inadequate circulation.

The clinician concerned with the management of patients in coma after resuscitation often has to consider how long to persist with life supporting measures. His dilemma at one stage is to decide between full intensive care with artificial ventilation, proper correction of fluid balance etc. and the alternative, i.e. ventilation must be discontinued because of apparent fatal prognosis. These decisions depend on his ability to predict the course and outcome, which in turn involves an evaluation and integration of clinical findings and a variety of investigations. Without any factual base such decisions may be hazardous. Furthermore, the situation may be complicated if the physician has limited resources of intensive care at his disposal. In our study 115 respirator days during five years were used for patients who later succumbed. If accurate predictions of the outcome could be decided one day after resuscitation, 89 days in the ICU could have been reallocated. The discriminatory power of Bayes' theorem on our patients seemed no better than the depth of coma after 24 hours' treatment. However, added to the observation of the coma depth it could give further valuable indication of the individual prognosis.

During the last decade several studies have evaluated the predictive value of individual factors in patients with coma (7, 11, 12, 20, 21). A review of the literature with respect to prognosis after cardiac arrest and coma in view of our own results gives the following conclusions:

1. Coma per se after cardiac arrest is an unfavourable sign. In a series of 284 resuscitated patients with cardiac arrest Bell and Hodgson (2) reported that only 19% of comatose patients lived to

be discharged from hospital compared with 54 non comatose patients.

2. The duration of the postanoxic coma is a useful prognostic sign. Bokorjic and Buchthal (4) found that clinical recovery was complete in 90% of patients who had been comatose for less than 48 hours. In our series 12 of 13 patients in coma less than 24 hours lived to be discharged. Although the majority of reports of prognosis after postanoxic coma postulates that 2-3 days with persistent coma usually indicates a fatal outcome, there are exceptions. Norris and Chandrasekar (16) reported a patient with coma persisting for five days after cardiac arrest due to a myocardial infarction with VF in whom no residual intellectual or functional impairment was present 6 months later.

3. Age has no relation to the outcome. In the patients in medical coma reported by Caronna (6) age had no predictive value, which is in agreement with our findings. All our long term survivors above 75 years of age were discharged without sign of impaired brain function.

4. The electroencephalogram appears to be an accurate predictor of outcome (3, 15, 19) but an unacceptable frequency of false positive results has been reported (19). Furthermore, it is a tedious and time-consuming procedure not always available in routine care.

5. The prognostic value of neurological signs has been evaluated in several reports (6, 7, 12, 21). Most neurological signs may have potential predictive value: the oculovestibular response and the response to painful stimuli. Caronna and Plum found that an absent oculovestibular response always implied severe disability or death. Willwood and Leach (21) reported that patients in coma after cardiac arrest who were unresponsive or responded in a reflex fashion to painful stimuli

or survived with intellectual damage. In our series all long term survivors responded normally to painful stimuli while 20 of 38 short term survivors had an abnormal reaction 74 hours after cardiac arrest. An important observation is that the clinical state of motor decerebration may be reversible if the corneal and deep tendon reflexes are intact and if hypotension is absent (5). Caronna et al (6) found that the oculovestibular reflexes gave the best single prediction 93% of their patients with absent oculovestibular reflexes subsequently died. A combination of oculovestibular reflexes and motor response to noxious stimulation added to the predictive power. Non reactive pupils on admission or immediately after successful resuscitation gave no further information of prognostic value in our series. However persistent fixed pupils 24 hours after resuscitation appeared to be an indicator of fatal outcome.

Resumption of spontaneous respiration immediately after resuscitation appears to be of predictive value. Ten of 12 long term survivors in our series resumed spontaneous respiration compared with 4 of 38 short term survivors.

The results from our study show that approximately 4% of all patients admitted to an emergency room will be long term survivors. One of four patients with initially successful resuscitation will survive. In order to avoid unnecessary treatment in patients however we need better methods of prognostication on these patients.

## ACKNOWLEDGEMENT

This study was supported by a grant from the Swedish Council for Research in Health and Medical Sciences.

## REFERENCES

1. Baum R S, Alvarez H & Cobb L A. Survival after resuscitation from out of hospital ventricular fibrillation. *Circulation* 50: 1231 1974.
2. Bell J A & Hodgson H J. Coma after cardiac arrest. *Brain* 97: 361 1974.
3. Binnie C D, Prior P F, Lloyd D S L, Scott D F & Margenson J H. Electroencephalographic prediction of fatal anoxic brain damage after resuscitation from cardiac arrest. *Br Med J* 4: 265 1970.
4. Bokorji N & Buchthal F. Postanoxic unconsciousness

- ness as related to clinical and ECG recovery in stagnant anoxia and carbon monoxide poisoning. In *Cerebral anoxia and the electroencephalogram* (ed H Gastaut and J S Meyer) pp 118-125. Thomas Springfield 1961.
5. Brendler S J & Silverstone B. Recovery from decerebration. *Brain* 93: 381 1970.
6. Caronna J J, Leigh J, Shaw D, Carlidge N, Knoll Jones R & Plum F. The outcome of medical coma. Prediction by bedside assessment of physical signs. *Trans Am Neurol Assoc* 100: 25 1975.
7. Caronna J J & Plum F. Prognosis and medical coma. *Head Injuries* 1: 3 1976.
8. Cobb L A, Baum R S, Alvarez H & Schaffer N A. Resuscitation from out-of-hospital ventricular fibrillation: 4 years follow up. *Circulation* 51/52: 223 1975.
9. Folling M. Resuscitation i en medisk motlagelseavdeling. *Tidsskr Nor Lægeforen* 91: 1386 1971.
10. Hesse B, Jensen G & Sgurd B. Emergency room patients with cardiac arrest. *Dan Med Bull* 20: 30 1973.
11. Jennett B. Scale: scope and philosophy of the clinical problem. *Ciba Found Symp* 34: 3 1975.
12. Jennett B, Teasdale G, Braakman R, Minderhoud J & Knoll Jones R. Predicting outcome in individual patients after severe head injury. *Lancet* i: 1031 1976.
13. Lawrie D M, Greenwood T N & Goddard M A. Coronary care unit in the routine management of acute myocardial infarction. *Lancet* 2: 109 1967.
14. Lund I & Skulberg A. Resuscitation of cardiac arrest out of hospitals. Experiences with a mobile intensive care unit in Oslo. *Acta Anaesthesiol Scand (Suppl)* 53: 13 1977.
15. Møller M, Holm B, Søndrup E & Lyager Nilsen B. Electroencephalographic prediction of anoxic brain damage after resuscitation from cardiac arrest in patients with acute myocardial infarction. *Acta Med Scand* 203: 31 1978.
16. Norris J R & Chandrasekar S. Anoxic brain damage after cardiac resuscitation. *J Chron Dis* 24: 585 1971.
17. Pantridge J F. Mobile coronary care. *Chest* 58: 229 1970.
18. Peatfield R C, Taylor D, Silett R W & McColl H W. Survival after cardiac arrest in hospital. *Lancet* i: 1223 1977.
19. Prior P F. The ECG in acute cerebral anoxia. *Excerpta Medica*. Amsterdam 1973.
20. Teasdale G & Jennett B. Assessment and prognosis of coma after head injury. *Acta Neurochir* 34: 45 1976.
21. Wloughby J O & Leach B G. Relation of neurological findings after cardiac arrest to outcome. *Br Med J* 3: 437 1974.



# Work Status after Coronary Bypass Surgery

*A Prospective Randomized Study with Ergometric and Angiographic Correlations*

M H Frick P-T Harjola and M Valle

*From the Cardiovascular Laboratory First Department of Medicine Third Department of Surgery and the Department of Diagnostic Radiology University Central Hospital Helsinki Finland*

**STRACT** The rate of return to work was assessed in a series of patients with coronary heart disease randomly allocated to medical and surgical treatment groups of 50 patients each. Sixteen of the medical and 10 of the surgical patients were already retired at entry and did not resume work later. Only 9 patients (18%) on medical therapy were working at 2 years follow-up in contrast to 18 (60%) working after bypass surgery ( $p < 0.05$ ). Functional classification of angina pectoris and exercise tolerance on ergometry were significantly better in the surgical group, especially in the surgical subgroup at work. Repeated operative angiographies of the inserted grafts and native vessels disclosed that completeness of atherosclerotic disease was related to work status after bypass surgery. The data suggest that a combination of coronary bypass surgery and medical therapy when indicated is superior to medical therapy alone in influencing the rate of working in coronary heart disease.

**Keywords:** coronary heart disease coronary angiography exercise testing

Acta Med Scand 206 61 1979

Coronary bypass surgery results in marked relief of symptoms in the majority of patients (3, 12). This improved quality of life should affect the rate of return to work. However, the non-randomized studies that have addressed themselves to this problem (1, 2, 8, 10, 11, 13, 16) have shown that despite alleviation of symptoms fewer patients than expected have resumed work, the proportion ranging from 40 to about 80%. The motivation to return to work is evidently related to a number of considerations including the physician's attitude and the generosity of disability programs which differ from one community to another. It is therefore not rele-

vant to judge the return to work after bypass surgery without the analysis of a concomitant randomized group subjected only to medical therapy.

We report the rate of return to work after coronary bypass surgery in a randomized series followed prospectively.

## PATIENTS AND METHODS

One hundred male patients under the age of 65 were randomly allocated into two groups of 50 each. The criteria for inclusion and exclusion as well as the randomization process have been reported earlier (15). The basic requirements were angina pectoris which did not respond satisfactorily to medical therapy including  $\beta$  blockade and short- and long-acting nitrates, at least a 2-vessel disease revealed by coronary angiography and good left ventricular function (ejection fraction  $\geq 50\%$ ). One group received medical therapy alone, the other coronary bypass surgery and medical therapy when indicated. A comparison of the groups with regard to the severity of angina, the prevalence of past myocardial infarctions, the degree of coronary atherosclerosis, left ventricular function and exercise tolerance at entry did not reveal any significant differences.

The severity of angina pectoris was graded as follows: 1 = no angina; 2 = angina when walking uphill/upstairs; 3 = angina when walking rapidly on the level; 4 = angina when walking slowly on the level; and 5 = grade 4 + occasional pain at rest. Patients with intractable angina were not randomized. Exercise testing was performed with an electrically braked bicycle ergometer up to the subjective maximum consisting of angina requiring trinitrin as earlier described (4). In a number of patients who were asymptomatic postoperatively the test was discontinued at a heart rate exceeding 85% of the age-predicted maximum. In the testing at entry, treatment with  $\beta$  blocking drugs was discontinued at least a week before the test. In the subsequent testing these compounds were allowed. The exercise tolerance is reported as the maximal tolerated load in kNm ( $= 102$  kpm/min).

Postoperative selective coronary angiographies were performed at 3 weeks, 1 year and 5 years after the opera-



Table I Characteristics of patients working at entry

	Medical group	Surgical group
No of pats	34	30
Physically demanding jobs	11 (32%)	13 (43%)
Age (y)*	46.3 ± 6.9	48.5 ± 5.7
Functional class*	3.4 ± 0.9	3.5 ± 0.8
Maximal load (kNm/min)*	5.6 ± 2.1	5.8 ± 2.2
No. and % of pats on $\beta$ blockers	30 (88%)	26 (87%)
Rate of retirement		
6 mo	1 dead 13 retired 20 at work	8 retired 22 at work
12 mo	3 dead 18 retired 13 at work	10 retired 20 at work
24 mo	4 dead 21 retired 9 at work	12 retired 18 at work

Mean  $\pm$  S.D. of the mean

tion. Both the grafts and the native vessels were injected to assess the progression of disease in the coronary arteries (5). Completeness of revascularization was deemed to exist if: 1) all significant ( $\geq 50\%$ ) lesions were bypassed; 2) none of the grafts were occluded; 3) no new significant lesions developed in the ungrafted arteries; 4) no new significant lesions developed distal to graft anastomosis. The medical group was first subjected to repeated angiography after 5 years follow up.

The patients were studied clinically and with exercise testing at 6-month and 1 year follow up and annually thereafter. The follow up times range from 2 to 5 years with a 100% follow up at 2 years, which forms the cut off point of this report.

## RESULTS

At entry into the trial 16 patients in the medical group and 19 in the surgical group were permanently retired. One patient in the surgical group refused to undergo the operation. This left 34 patients in the medical and 30 in the surgical group to be followed with regard to work status. None of the patients retired at entry resumed work later. There were no significant differences in the characteristics of the medical and surgical groups (Table I). As is evident from Table I, there was no perioperative or postoperative mortality in the surgical group, whereas 4 patients (12%) died in the medical group during the follow up. At 2 years, 9 (26%) of 34

medical patients were working in contrast (60%) of 30 surgical patients (Fig. 1). If the are included, the difference is significant at 1 level ( $\chi^2=6.035$ ); if the deaths are excluded, significant at the 5% level ( $\chi^2=4.304$ ). In both groups the work status was dichotomous: at or retirement without a clear trend to permanent employment or a change to less demanding jobs.

The characteristics of the relevant subgroups given in Table II. The only significant difference between the medical group was the better functional class of the patients at work. In the surgical group, patients at work were some 4 years younger and maximal tolerated load c. 70% higher than the retired patients. The surgical group had a better overall functional classification; the retired surgical patients differed significantly from the retired medical patients ( $t=3.473$ ,  $p<0.001$ ) but not the medical patients at work; the surgical work differed significantly from both the medical patients at work ( $t=6.810$ ,  $p<0.001$ ) and the retired patients at work ( $t=3.125$ ,  $p<0.01$ ). This applied to the maximal load of the surgical patients at work, whereas the mean maximal load of retired surgical patients was almost the same as of the retired medical patients.

Repeated coronary angiography in the surgical group revealed that only 3 (25%) of the 12

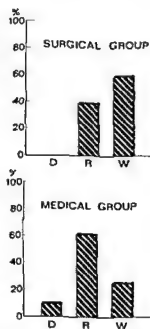


Fig. 1 Proportions of patients deceased (D), retired and working (W) after 2 years follow up.

Table II Characteristics of the study groups at 2 year follow up

	Medical group			Surgical group		
	Retired (n=21)	At work (n=9)	p	Retired (n=12)	At work (n=18)	p
Physically demanding jobs (y)	9 (43%)	2 (22%)	ns	7 (58%)	6 (33%)	ns
Functional class*	46.7±4.7*	48.0±9.0	ns	47.9±5.3	43.5±4.8	<0.05
Maximal load (kNm/min)	3.7±0.7	2.8±0.7	<0.01	2.3±1.3	1.8±1.0	ns
Maximal load and % of patients on β-blockers	5.5±2.3	6.6±2.9	ns	5.3±2.9	8.9±2.4	<0.001
β-blockers	21 (100%)	8 (89%)	ns	5 (42%)	12 (67%)	ns

\*mean ± S.D. of the mean

†Not significant ( $p>0.05$ )

Patients were completely revascularized whereas 7% of the 18 patients at work exhibited complete revascularization ( $\chi^2=4.185$   $p<0.05$ )

## DISCUSSION

A weakness is easily discernible in our study—small sample size. However, its impact on the reliability of the data would appear only if the composition of the series deviates considerably from the population at large. When the present study was started in 1973 and for some years thereafter, our institution was the only one in Finland performing coronary bypass surgery. This meant that we recruited patients from the whole country including farmers and lumberjacks engaged in heavy manual

The proportion of patients in physically demanding jobs is fairly high (Table I); the surgical group exhibiting a prevalence some 10% higher than the medical group. This excludes the possibility that the significantly higher rate of return to work after coronary bypass surgery could be due to differences in the distribution of occupations. The functional classification of angina based on patients' own testimony is prone to inaccuracy. In the present study the functional classes of the different subgroups (Table II) were nicely paralleled by the data on exercise testing, which clearly showed the superiority of the surgical subgroup at rest. It should be noted, however, that a fairly high proportion of the surgical patients were on β-blockers because of residual angina, arrhythmias, hypertension or combinations of these. According to the difference observed in the rate of return to work and in other factors reflects the effect of bypass surgery and additional medical therapy as indicated over medical therapy alone.

The motivation to work with manifest coronary heart disease is related to a number of variables: physical, emotional and socioeconomic. It is anticipated that these are evenly distributed in a series with random design. This might not be true, however, since the medical subset is deprived of the currently fashionable mode of surgical therapy and this may adversely affect the emotional components of work motivation. This factor may be operative in the present study since the retired medical patients had a significantly poorer functional classification than the retired surgical patients despite similar exercise tolerance on ergometry (Table II). The anatomical substrate for the difference in the subjective and objective exercise tolerance between the two surgical subgroups was evidently the degree of revascularization. Both groups share the other potential factors evoking pain relief, e.g. the placebo effect, pericoronary denervation etc. (3). The completeness of the revascularization was assessed on the basis of findings at two postoperative angiographies but not exactly at 2 years after the operation. There is a great deal of evidence that the majority of graft occlusions occur very early with a low rate of further attrition (4, 7, 9). The changes in native arteries may, however, develop and progress continuously (5, 6), introducing an unknown component into our series between 1 and 2 years of follow up.

Dissatisfaction can be expressed about the rate of resuming work after coronary bypass surgery. The reasons for the discrepancy between reality and expectations are certainly numerous and not least based on local socioeconomic conditions. The present study with random design clearly suggests that coronary bypass surgery coupled with medical therapy, when indicated, results in a higher rate of

working than medical therapy alone in a series of patients fulfilling the entry criteria outlined

### ACKNOWLEDGEMENT

This study was supported in part by a grant from the Finnish State Council for Medical Research

### REFERENCES

- 1 Barnes G K, Ray M J, Oberman A & Kouchoukos N T. Changes in working status of patients following coronary bypass surgery. *JAMA* 238 1259 1977
- 2 Fox H E, May I A & Ecker R R. Long term functional results of surgery for coronary artery disease in patients with poor ventricular function. *J Thorac Cardiovasc Surg* 70 1064 1975
- 3 Frick M H. An appraisal of symptom relief after coronary bypass grafting. *Postgrad Med J* 52 765 1976
- 4 Frick M H, Hagola P T & Valle M. Effect of aortocoronary grafts and native vessel patency on the occurrence of angina pectoris after coronary bypass surgery. *Br Heart J* 37 414 1975
- 5 Frick M H, Valle M, Hagola P T & Korhola O. Changes in native coronary arteries after coronary bypass surgery. Role of graft patency, serum lipids and hypertension. *Am J Cardiol* 36 744 1975
- 6 Griffith L S C, Achuff S C, Conti C R, Humphries J O, Brawley R K, Gott V L & Ross R S. Changes in intrinsic coronary circulation and segmental ventricular motion after saphenous vein coronary bypass graft surgery. *N Engl J Med* 288 589 1973
- 7 Grondin C M, Lespérance J, Bourassa M G, Pasternac A, Campeau L & Grondin P. Angiographic evaluation in 60 consecutive patients with aorto-coronary artery vein grafts 2 year and 3 years after operation. *J Thorac Cardiovasc Surg* 67 1 1974
- 8 Hoel B, Eie H, Semb G & Sivertsen J. Aortocoronary vein bypass in patients with angina. *Acta Med Scand* 197 383 1975
- 9 Lawrie G M, Lie J T, Morris G C Jr, Ley H L. Vein graft patency and intima after aortocoronary bypass. Early and long angiopathologic correlations. *Am J Cardiol* 1976
- 10 Lichtlen P, Liese W, Leitz K & Borst H. Postoperative Klinik nach aorto-koronarem Bypass in Relation zum Ausmass der Revaskularisation. *Z Kardiol* 67 83 1978
- 11 Logue D B, King S B & Douglas S J. A practical approach to coronary artery disease. A special reference to coronary bypass surgery. *Probl Cardiol* 1 1 1976
- 12 McIntosh H D & Garcia J A. The first aortocoronary bypass grafting 1967-1977. *Circulation* 57 405 1978
- 13 Reul G J, Morris G C Jr, Howell J I, Ford E S & Stelter W J. Current results of coronary artery surgery. A critical analysis of patients. *Ann Thorac Surg* 14 243 1972
- 14 Rimm A A, Barboriak J J, Anderson J S, Simon J S. Changes in occupation after aortocoronary vein bypass operation. *JAMA* 236 361 1976
- 15 Varnauskas E & Olson S B. The European center CABG trial. In: *Progress in cardiovascular surgery* (P N Yu & J F Goodwin) p 83. Lea & Febiger, Philadelphia 1977
- 16 Verhies W, Pressens J, Suy R, Kestebeek H, De Geest H. Initial experience with aortocoronary bypass graft surgery. A follow up study. *Acta Med Scand* 197 32 157 1977

# Mortality, Arrhythmias and Pump Failure in Acute Myocardial Infarction in Relation to Estimated Infarct Size

R Nordlander and O Nyquist

*From the Department of Medicine Karolinska Institutet at Huddinge Hospital Huddinge Sweden*

**ABSTRACT** Serial estimations of total serum creatine kinase (S-CK) were made in 194 consecutive patients with acute myocardial infarction (AMI). By using the maximum CK value could not separate patients in terms of high and low mortality but when the maximum CK value was related to age for patients with and without a history of previous AMI, subgroups became apparent: one with 46% mortality (high risk group) and another with 6% (low risk group) during the hospital stay plus the next 90 days. In 114 of the patients infarct size could be estimated. A good correlation was found between maximum CK and calculated infarct size ( $r = 0.93$ ). Calculated infarct size alone could not distinguish between high and low mortality but when it was related to age for patients with and without a history of AMI, two subgroups emerged, one with 46% mortality and another with 6% during the hospital stay plus the next 90 days. The incidence of ventricular tachycardia during the stay in the Coronary Care Unit did not differ between the two risk groups separated either by maximum CK value or estimated infarct size. However, the incidence of congestive heart failure and severe left heart failure during the acute phase was higher in the high risk group.

**Keywords:** acute myocardial infarction, infarct size, creatine kinase, prognosis, ventricular tachycardia.  
*Med Scand* 206: 65, 1979.

Serial determinations of total serum creatine kinase (CK) have been used to assess infarct size with aid of a computer program (19). A correlation has been found not only between infarct size and mortality (22) but also between infarct size and left ventricular function (10), left heart failure (13), frequency of ventricular arrhythmias (17) and ventricular fibrillation threshold after acute myocardial infarction (AMI) (2).

However, the method for calculating infarct size is complicated and requires a computer system that is not available to most hospitals. Recently preliminary results were presented for a simpler method for estimating infarct size and predicting mortality risk. By combining the maximum CK value obtained from serial estimations of S-CK, age of the patient and history of previous AMI, two subgroups could be discerned: one with 46% and another with 6% hospital plus three month mortality (6). In the present study that series of patients has been extended and a linear discriminant analysis has been used to separate patients with different mortality risks. For comparison, infarct size has also been calculated by a computer program according to Sobel et al. (23). The frequency of arrhythmias and pump failures in the total series and in the different risk groups has also been studied, as well as mortality in relation to the different complications and risk groups.

## PATIENTS AND METHODS

Consecutive patients admitted to the Coronary Care Unit (CCU) within 48 hours after onset of symptoms consistent with AMI were included in the study. The diagnosis of AMI was based on: 1) appearance of a pathologic Q wave and/or appearance or disappearance of a localized ST elevation followed by a T inversion and/or 2) two raised

**Abbreviations:** CK = creatine kinase, S-CK = serum CK, AMI = acute myocardial infarction, CCU = coronary care unit, S-ASAT = serum aspartate aminotransferase, S-ALAT = serum alanine aminotransferase, ECG = electrocardiogram, VT = ventricular tachycardia, ISO = observed infarct size.

**Address for reprints:** R Nordlander, M.D., Department of Medicine, Huddinge Hospital, S-141 86 Huddinge, Sweden.

S-ASAT (serum aspartate aminotransferase) values with a maximum about 24 hours after onset of symptoms in association with lower S-ALAT (serum alanine aminotransferase) values with a maximum after about 36 hours. 3) findings at autopsy of myocardial necrosis of an age corresponding to the onset of symptoms.

A 12 lead electrocardiogram (ECG) was registered on admission and each morning during three days. A continuous one lead ECG was monitored on an oscilloscope and recorded by an ink jet recorder as long as the patient stayed in the CCU. Arrhythmias were noted in a data chart.

The patients were examined clinically at least three times daily. Heart rate, blood pressure and respiratory rate were recorded every hour. These results were also recorded in the data chart. All injections in the CCU were given intravenously.

Serum samples for estimation of S-ASAT and S-ALAT were taken on admission at 8 a.m. and 8 p.m. daily during three days. Serum samples for estimation of S-CK were taken on admission and then every two hours during the first 12 hours and every four hours during the next 12–24 hours. The sample was centrifuged and the serum was frozen to  $-18^{\circ}\text{C}$  for 1–3 days. The CK activity expressed in mU/ml (4) was measured at  $37^{\circ}\text{C}$  with a spectrophotometric method described by Oliver (15) and modified by Rosalki (18). The relative methodological error obtained from double samples was 7%. Comparison of CK activity in samples analysed immediately and after freezing showed no significant differences. Only CK curves starting below an S-CK level of 400 mU/ml were accepted in the study.

#### Definitions

**Supraventricular tachyarrhythmia.** Onset of sinus tachycardia, atrial tachycardia, atrial flutter, atrial fibrillation or nodal tachycardia. **Supraventricular bradyarrhythmia.** Onset of sinus bradycardia, sinus arrest or nodal rhythm. **Ventricular tachycardia (VT).** Three or more ventricular ectopic beats in succession. **Hypotension.** A systolic blood pressure of 90 mmHg or below. **Shock.** Hypotension in combination with at least three of the following criteria: 1) oliguria, 2) deterioration of sensorium, 3) cold skin, 4) cyanosis and 5) acidosis. **Moderate left heart failure.** Basal pulmonary crepitant rales. **Severe left heart failure.** Rales up to scapula or frank pulmonary oedema.

**CK maximum.** The highest value reached. Fourteen curves were still rising when the sampling was discontinued. These curves will be discussed separately. No curves started with the maximum value.

**Infarct size** was calculated according to Sobel et al. (23) by a computer program. For optimal results with this method only CK curves starting from a normal value (100 mU/ml,  $37^{\circ}\text{C}$ ) were accepted. The calculated infarct size in accordance with Sobel et al. is termed *observed infarct size* (ISO) and expressed in CK gram equivalents (CK gEq).

#### Statistical methods

The statistical calculations have been made with the  $\chi^2$  test with Yates's correction or Student's *t* test. Separation

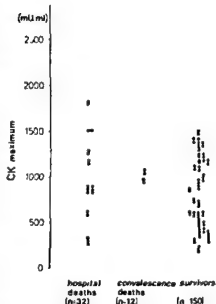


Fig. 1 CK maxima for hospital deaths, convalescence deaths (3 months) and survivors.

of the risk groups was done with a linear discriminant analysis (BMD04M, Health Sciences Computing, UCLA).

## RESULTS

During the period of investigation 241 patients were treated in the CCU. Eight patients in severe circulatory distress on admission had serum samples for estimation of S-CK obtained. None of them survived for more than one hour in the CCU. A further 39 patients were excluded because their CK curves started with a serum level of 400 mU/ml. Remaining 193 patients, 139 men and 55 women, aged 39–74 (mean 64). Fifty per cent of the patients were treated within 3 hours from onset of symptoms. Four (33%) had a history of a previous AMI. Two patients (16%) died in hospital and 12 within three months, giving a combined plus three month mortality of 23%. None had given intramuscular injections before admission. The maximum value for S-ASAT was  $3.22 \mu\text{kat/l}$ , S-CK 983 mU/ml.

CK curves which started from a normal value were found in 114 patients and these curves were used to calculate the ISO. These patients differ from the total series regarding age, sex, distribution, history of previous AMI or enzymuria. However, there was a tendency toward

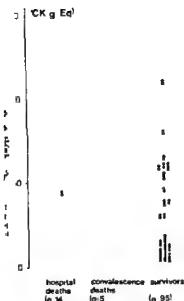


Fig. 2 CK maximum (g Eq) for hospital deaths (n=14), convalescence deaths (n=5) and survivors (n=95).

mortality in this group although the difference was not significant compared with the total series. Seventeen of the 114 patients (17%) died within three months.

Figure 1 shows that the CK maxima for hospital deaths and convalescence (three months) deaths and survivors are within the same range. Figure 2 illustrates the same for ISO. Figure 3 shows the correlation between CK maximum and ISO ( $r=0.93$ ) (Fig. 3).

It is obvious from Figs. 1 and 2 that neither CK maximum nor ISO can be used for individual prognostics of mortality. However, when CK maximum and ISO are related to age for patients with or without a previous history of AMI, discriminant analysis can separate two groups with different mortalities (Fig. 4). For patients without a history of previous AMI, the mortality in the high risk group (above the discriminating line—the risk line) is 25% (25/27) and in the low risk group (below the risk line) 3% (2/73). For patients with a history of previous AMI, the corresponding figures are 50% (24/47) and 13% (5/40). Altogether the hospital plus convalescence (3 months) mortality in the high risk group is 46% (37/81) and in the low risk group 6% (13/213). The corresponding figures for CCU mortality are 26 vs. 3% and for hospital mortality 35 vs. 1%. All these differences are statistically significant ( $p < 0.001$ ).

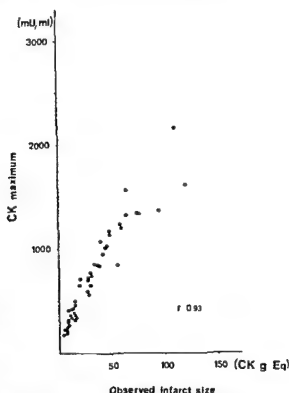


Fig. 3 Correlation between CK maximum and ISO calculated by the computer method.

Figure 5 illustrates the same method of separation when ISO is related to age for patients with or without a history of previous AMI. For patients without a history of previous AMI, the mortality in the high risk group is 39% (10/26) and in the low risk group 0% (0/47). The corresponding figures for patients with a history of previous AMI are 47% (7/15) and 8% (2/26). Altogether the mortality in the high risk group is 42% (17/41) and in the low risk group 3% (2/73). The corresponding figures for both CCU mortality and hospital mortality are 34% vs. 1%. All differences are statistically significant ( $p < 0.001$ ).

Table I shows the total frequency of arrhythmias and pump failure and these complications in the risk groups separated by either CK maximum or ISO in combination with age and history of previous AMI. Table II illustrates the mortality in relation to the different complications in these risk groups. As can be seen from the tables, the results were essentially the same when CK maximum or ISO was used for separation, with no statistically significant differences.

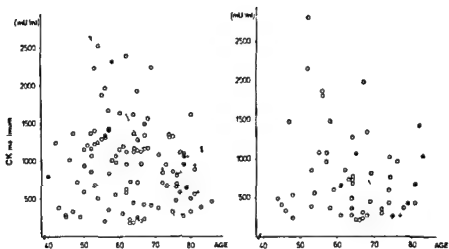


Fig. 4 CK maximum to age for patients (right) and without (left) history of previous AMI. The discriminating line separates the high risk (above the dotted line) from the low risk groups (below the dotted line). O = survivors, + = hospital deaths, ⊗ = convalescent deaths.

## DISCUSSION

A small number of patients in severe circulatory distress on admission were excluded from the study which may explain the somewhat low mortality. An interesting finding was the tendency towards a lower mortality in the 114 patients with CK curves starting from a normal value. These patients had a tendency towards a shorter delay between the onset of symptoms and admission to the CCU which perhaps contributes to the lower mortality. Apart from this the 114 patients seemed to be representative of the total material.

The prognosis after an AMI seems to depend at least partly upon the mass and quality of the remaining viable myocardium. In previous series a

correlation has been found between on the one hand enzyme maximum and on the other size and/or mortality (5, 9, 20, 21). In the present series CK maximum or ISO alone could not predict individual mortality. A good prediction was never obtained when the age of the patient and history of previous AMI were included. The influence of age has in previous studies been shown to be of great prognostic importance (1, 14, 15) and might be considered as a rough estimate of the quality of the remaining myocardium. The more the viable myocardium is reduced after an AMI, accordingly a raised mortality has been found after reinfarctions (7, 8). An interesting finding in the present series was a difference of about 100 mU/ml or 25 CK gEq between the discrim-

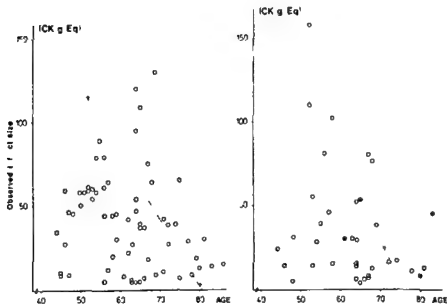


Fig. 5 ISO in relation to age for patients with (right) and without (left) a history of previous AMI. The discriminating line separates the high risk groups (above the dotted line) from the low risk groups (below the dotted line). Symbols as in Fig. 4.

# 1 Frequency (%) of complications in the total series and in the risk groups separated by CK maximum or ISO

cal differences are calculated between high and low risk groups separated by CK maximum or ISO respectively

	Total		High risk group		Low risk group		p
	CK max (n=194)	ISO (n=114)	CK max (n=81)	ISO (n=40)	CK max (n=113)	ISO (n=74)	
ventricular tachy- thmia	16	15	22	20	12	12	N S
ventricular brady- thmia	9	12	10	15	9	11	N S
ventricular fibrillation	41	40	48	45	36	37	N S
and degree and complete block	4	3	6	5	3	1	N S
ventricular standstill	10	7	19	15	4	1	<0.05/0.01
tension	7	5	15	13	2	1	<0.05
	13	18	17	28	10	14	N S
	5	5	11	13	1	1	<0.01
late left heart failure	47	47	46	43	39	47	N S
early left heart failure	14	12	26	28	5	4	<0.01

Comparison with CK maximum gives  $p < 0.05$  with ISO  $p < 0.01$

For patients with or without a history of previous AMI. This difference might be explained by the previous myocardial damage in the former patients. From the correlation between CK maximum and ISO and the almost identical separation of risk groups with these parameters it was concluded that CK maximum can be used as an estimation of infarct size if the CK samples are obtained serially. In an earlier series (19) a correlation coefficient of 0.8 was found between CK maximum and ISO but that series comprised only 11 patients.

CK maximum was obtained from serial estimations

and was defined as the highest value reached. However, this series includes 14 curves that were still rising when the sampling was discontinued. This has no influence on prognostic evaluation in the ten cases in whom the CK curves ended above the risk line separating the high and low risk groups (Fig. 4) since these patients were already classified as high risk cases. However, the possibility of being erroneously classified as false low risk cases exists in the four patients whose CK curves ended below the risk line.

The total frequency of complications was in accordance

## Table II Three month mortality (% of patients with respective complication) in relation to different categories in the total series and in the risk groups separated by CK maximum or ISO

	Total		High risk group		Low risk group	
	CK max	ISO	CK max	ISO	CK max	ISO
ventricular tachy- thmia	39	24	67	50	0	0
ventricular brady- thmia	22	14	38	33	10	0
ventricular fibrillation	76	24	41	50	13	7
and degree and complete block	75	33	80	50	66	0
ventricular standstill	55	63	67	67	20	50
tension	100	100	100	100	100	100
shock	16	38	29	64	0	10
late left heart failure	90	100	89	100	100	100
early left heart failure	23	19	43	41	7	6
cardiac material	48	36	57	45	17	0
cardiac material	23	17	46	43	6	3



cordance with findings of previous authors (8) Roberts et al (17) found an increasing incidence of ventricular arrhythmias with increasing infarct size calculated by the computer method. Mogensen (11) found a correlation between the maximal S-ASAT value and the incidence of VT. Chapman (3) observed an association between the incidence of both supraventricular and ventricular arrhythmias and the rise in serum transaminase levels. Also in the present series patients with VT had higher CK maxima (mean 1100 mU/ml) than those without (mean 891 mU/ml) ( $p < 0.05$ ) but the incidence of VT did not differ in the two risk groups. However the mortality among patients with VT in the high risk group was significantly higher ( $p < 0.05$ ) than among patients with VT in the low risk group. The figures were essentially the same when the risk groups were separated by ISO, age and history. Thus a VT per se was not associated with an increased mortality but if it was combined with a high CK maximum (or ISO) and/or advanced age the mortality did increase.

The incidence of shock and severe left heart failure was significantly increased in the high risk groups separated either by CK maximum or ISO which is in accordance with the findings of Norris et al (13) who found an increasing incidence of left heart failure with increasing infarct size measured by the computer method. Sjögren (20) also found an increasing incidence of left heart failure with increasing S-ASAT maxima. Shock and severe left heart failure were also associated with a higher mortality rate in our total series. However there were too few patients with these complications in the low risk groups to permit comparison between the associated mortality in the different risk groups.

Separating with both CK maximum or ISO gave a significant overrepresentation of second degree AV block, complete AV block and ventricular standstill in the high risk groups. These complications were also associated with an increased mortality in the total material but the numbers were too small in the low risk groups to permit further conclusions. Ventricular standstill was a complicating arrhythmia in all cases with 100% mortality.

There were eight cases of ventricular fibrillation evenly distributed among the high and low risk groups. The mortality figures associated with this complication were essentially equal in the different risk groups, although the numbers were too small to permit conclusions.

The incidences of hypotension, moderate heart failure and supraventricular bradyarrhythmias were of the same magnitude in the different groups. The mortality associated with these complications did not differ from the mortality in the total series. Patients with supraventricular bradyarrhythmia were also evenly distributed in the risk groups but the high risk patients had a higher mortality than those in the low risk group with the same complication.

## CONCLUSIONS

There was a good correlation between CK maximum obtained from serial estimations of S-ASAT and ISO. By themselves CK maximum or ISO were good predictors of mortality after AMI. The combination of CK maximum (or ISO), age of patient and history of previous AMI separated a high risk group of patients with 46% (42%) hospital and three month mortality after AMI from a low risk group with only 6% (3%) mortality. In the high risk groups there was an overrepresentation of patients with severe left heart failure and shock, in contrast to VT which was evenly distributed among patients with high and low mortality risk.

## ACKNOWLEDGEMENT

This study was supported by grants from the National Association against Heart and Chest Disease.

## REFERENCES

1. Björck G, Blomqvist G & Sievers J. S-ASAT myocardial infarction in Malmö 1935 to 1955. *Med Scand* 159: 253, 1957.
2. Bloomer C M, Ehsani A, White F C & Sobel P H. Ventricular fibrillation threshold in acute myocardial infarction and its relation to myocardial infarction. *Cardiovasc Res* 9: 468, 1975.
3. Chapman B L. Relation of cardiac complex S-GOT level in acute myocardial infarction. *JAMA* 234: 890, 1972.
4. Enzyme nomenclature. Recommendations 1960. International Union of Biochemistry. I. Amsterdam, London and New York, 1965.
5. Erhardt L R. Clinical and pathological observations in different types of acute myocardial infarction. *Med Scand (Suppl)* 560, 1974.
6. Forsell G, Nordlander R, Nyquist O, Onnerby A & Styrelius I. Prediction of mortality risk in

- Myocardial infarction (Abstract) *Br Heart J* 58 531 1976
14. Elmers C Short and long term prognostic indices in acute myocardial infarction *Acta Med Scand (Suppl)* 555 1973
15. Jennings R & Lundman T Swedish co-operative CU study *Acta Med Scand (Suppl)* 586 1975
16. Olsson O & Nilsson N J Observations on the diagnostic and prognostic value of some enzyme tests in myocardial infarction *Acta Med Scand* 182 597 1967
17. Pathy D Bleifeld W Hanarath P & Effert S Attempt to quantitate relation between cardiac function and infarct size in acute myocardial infarction *Br Heart J* 36 271 1974
18. Jørgensen L Ventricular tachyarrhythmias and lignocaine prophylaxis in acute myocardial infarction *Acta Med Scand (Suppl)* 513 1970
19. Nordlander R Creatine phosphokinase in acute myocardial infarction Thesis Stockholm 1976
20. Morris R M Brandt P W T Caughey D E Lee A J & Scott P J A new coronary prognostic index *Lancet* i 274 1969
21. Morris R M Whithlock R M L Barrat Boyes C & Small C W Clinical measurement of myocardial infarct size *Circulation* 51 614 1975
22. Oliver I T A spectrophotometric method for the determination of creatine phosphokinase and aspartate kinase *Biochem J* 61 116 1955
23. Peel A A F Semple T Wang I Lancaster W M & Dall J L G A coronary prognostic index for grading the severity of infarction *Br Heart J* 24 745 1967
24. Roberts R Husain A Ambos H D Oliver G C Cox J R & Sobel B E Relation between infarct size and ventricular arrhythmia *Br Heart J* 37 1169 1975
25. Rosalki S B An improved procedure for serum creatine phosphokinase determination *J Lab Clin Med* 69 696 1967
26. Shell W E Kjekshus J K & Sobel B E Quantitative assessment of the extent of myocardial infarction in the conscious dog by means of analysis of serial changes in serum creatine phosphokinase activity *J Clin Invest* 50 2614 1971
27. Sjogren A Left heart failure in acute myocardial infarction *Acta Med Scand (Suppl)* 510 1970
28. Sobel B E Applications and limitations of estimation of infarct size from serial changes in plasma creatine phosphokinase activity *Acta Med Scand (Suppl)* 587 151 1975
29. Sobel B E Bresnahan G F Shell W E & Yoder R D Estimation of infarct size in man and its relation to prognosis *Circulation* 46 640 1972
30. Sobel B E Markham J Larsson K B User's guide for infarct size prediction program Monograph no 269 Washington University School of Medicine 1975



# The Q-T Syndrome—A Family Description

P. Andersson and L. Lundkvist

*From the Department of Medicine Huddiksvall Hospital Huddiksvall Sweden*

**TRACT** This paper describes a family of nine of whom five suffer from the surdocardiac syndrome. All five are deaf mute and have medical histories typical of the syndrome with frequent syncope attacks during the childhood, often caused by stress. Two of these five siblings have not suffered from single attacks since puberty and are still alive. The other three had had continuous frequent attacks into adult years and died in connection with syncope at 20, 27 and 37 years of age. The diagnosis, pathogenesis, treatment and genetics of the syndrome is discussed.

**words** Q-T syndrome hereditary diseases electrocardiography

Med Scand 206 73 1979

In 1957 Jervell and Lange Nielsen described a family with the Q-T syndrome (8). The syndrome is characterized by 1) Arrhythmias which may or may not be accompanied by angina pectoris syncope attacks and death 2) A prolonged Q-T interval in the ECG 3) Familial occurrence 4) Congenital deafness (surdocardiac type).

In 1963 two families were described both having similar syndrome but all members of which had normal hearing (Romano-Ward type) (14, 15). In 1972 a family with the long Q-T syndrome was described whose affected members either had normal or reduced high frequency hearing (11). Several cases of the syndrome occurring in Sweden have been described in published articles but most of these cases have been from different families (10). The different types of the syndrome appear to have similar genetic backgrounds with separate inheritance of hearing and heart lesion (11). It has been surmised that the syndrome with total deafness is inherited through an autosomal recessive mechanism whilst the syndrome without deafness

is inherited through an autosomal dominant mechanism.

This paper describes a family consisting of nine brothers and sisters of whom five are deaf. Two of these five siblings died without ECG being recorded. The ECGs of the other three had clearly prolonged Q-T intervals. The health of the family's parental generation and of the family's offspring and their children has been investigated to a certain extent. This paper is based upon anamnestic information from our patient upon correspondence with his brothers and sisters and upon extracts from medical journals.

## CASE REPORT

Our patient (IV 8) is a man born in 1922. He is a fraternal twin and has been deaf mute since birth. Both his parents who were cousins had normal hearing and had never suffered from syncopal attacks. The same applied to his four great grandparents and to the father's 11 brothers and sisters.

The patient has since childhood suffered from fainting attacks lasting for about one minute. The attacks were often associated with strenuous physical activity or occurred when he became frightened or excited. They were not accompanied by seizure or by passing of urine or faeces. He had had attacks during his youth until the age of 17. At this age the attacks ceased and did not recur until he was 52. Then he suddenly fainted 10-12 times on the same day and was admitted to hospital.

On admission he had auricular fibrillation that quickly changed to sinus rhythm with occasional ventricular ectopic beats. After having fainted again he was transferred to the Intensive Care Unit for observation but suffered no further attacks there. The ECG showed signs of an antero-septal infarction and the enzymes were slightly raised. He was discharged from hospital after 2 weeks and has suffered no further syncopal attacks since then.

He is now being treated with propranolol 40 mg  $\times$  3. ECG shows a corrected Q-T interval of 0.52 sec (0.54/55) (Fig. 1) and also an AV block I which may be caused by the  $\beta$  blockade therapy. The blood electrolytes are nor-

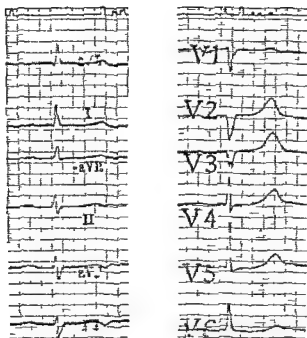


Fig 1 ECG from our patient (IV 8)

mal. The audiogram shows an almost complete neuro-genic hearing defect (Fig 2)

### DESCRIPTION OF THE FAMILY

The Q-T interval in the following text is shown as a corrected Q-T interval according to the formula: corrected

Q-T interval =  $QT/\sqrt{RR}$  (11). The upper limit is 0.44 sec. The measured Q-T and the heart rate are given in parentheses after the corrected Q-T interval. The families I 1-2, II 1-4 and III 2, 4-13 had no symptoms of the syndrome but have not been examined. III 4 and III 8, from whom we have ECGs. The interval of III 4 is 0.46 sec (0.42/72) and of III 8 (0.38/75) (Fig 3).

III 1. The mother had had normal hearing and suffered from fainting attacks. She died of heart failure at the age of 86. An ECG examination just before death revealed right bundle branch block with a Q-T interval of 0.48 sec (0.42/75). No audiogram is available.

III 3. The father had also had normal hearing and no syncopal attacks during his lifetime. An ECG taken just before his death showed right bundle branch block with a Q-T interval of 0.48 sec (0.38/95). No audiogram is available.

IV 1. A woman, deaf-mute since birth, who had attacks during childhood that continued into adulthood. She died in connection with a syncopal attack at the age of 37. The post mortem revealed no abnormalities. The microscopic examination of the heart showed patchy fibrosis with slight myocardial infiltration. An ECG recording taken just before death showed a Q-T interval of 0.60 sec (0.60/60). No record of blood electrolytes is available.

IV 2. A man with good hearing and no syncopal attacks. ECG shows a Q-T interval of 0.42 sec (0.42/65). An audiogram shows the same neuro-genic defect as in IV 3.

IV 3. A woman with good hearing (Fig 2) and no syncopal attacks. Her ECG recording shows a Q-T interval of 0.44 sec (0.42/70). An audiogram shows a normal frequency hearing as in presbycusis.

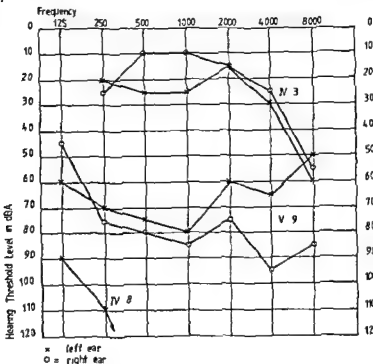


Fig 2 Audiograms of family members IV 3, IV 8 and V 9



and an unusually deformed T wave with varying amplitude the T wave may be positive, negative or biphasic. A normal ECG does not eliminate the possibility of the syndrome because the Q T changes can be intermittent (3). If the syndrome is suspected repeated ECGs should be taken and possibly also an exercise ECG (12). It should be noted however that a prolonged Q T interval can be seen in connection with other conditions not related to the syndrome for example in myocardial necrosis or with certain stimulations of the autonomic nervous system (6).

A prolonged Q T interval can also be seen in connection with ingestion of certain drugs such as quinidine in connection with hypokalemia or hypocalcemia in connection with cerebrovascular accidents or after Adams Stokes attacks (1-9). Q T changes related to the above conditions are however reversible. The cause of the heart symptom in the Q T syndrome is still unclear. In some cases primary damage to the myocardium has been suspected (7). Another theory is that an asymmetrical sympathetic stimulation of the myocardium occurs (16). With a prolonged Q T interval the refractory period is considerably longer in certain parts of the myocardium than in other parts. The difference in the length of the refractory period in different parts of the myocardium promotes the origin of ventricular fibrillation through the R on T phenomena (3).

The fact that the parents are cousins and that the syndrome occurs in only one generation strongly supports earlier observations that the surdocardiac syndrome has a recessive inheritance. The moderate prolongation of the Q T interval of unaffected members of the family (Fig. 3) may as Fraser et al. (2) postulated indicate that they are heterozygote carriers of the trait.

## REFERENCES

- Burch G E, Meyers R & Abildskov J A. A new electrocardiographic pattern observed in cerebrovascular accidents. *Circulation* 9: 719, 1954.
- Fraser G R, Froggatt P & Murphy T C. Aspects of the cardio auditory syndrome of and Lange Nielsen (congenital deafness, trocardiographic abnormalities). *Ann H* 28: 133, 1964.
- Furberg C & Hornell H. Familial Q T<sub>1</sub> and risk of sudden death. *Acta Paediatr Sc* 1975.
- Gale G E, Bosman C K, Tucker R B, Barlow J B. Hereditary prolongation of Q T interval: study of two families. *Br Heart J* 37: 505.
- Garza L A, Vick R L, Nora J J & McCall D G. Hereditary Q T prolongation without syncope. *Circulation* 41: 39, 1970.
- Han J, Garcia de Jalón P & Moe G K. The effects of ventricular vulnerability on the Q T interval. *Am Heart J* 1964.
- James T N. An etiologic concept concerning obscure myocardial pathologies. *Prog Cardiovasc Dis* 1964.
- Jervell A & Lange Nielsen F. Congenital deafness, functional heart disease with prolonged Q T interval and sudden death. *Am Heart J* 1957.
- Johansson B W. Adams Stokes syndrome: view and follow up study of forty two cases. *Cardiol* 8: 76, 1961.
- Johansson B W, Furberg C, Hennrich G J, Hornell H, Johansson B W, Ljung M, Malmberg L & Voigt G. The long Q T syndrome. *Lakartidningen* 72: 4620, 1975.
- Mathews E C, Blount A W Jr & Toole J H. Q T prolongation and ventricular arrhythmias in the same family. *Am Heart J* 29: 702, 1972.
- Philips J & Ichinose H. Clinical and experimental studies in the hereditary syndrome of prolonged Q T interval, syncopal spells and sudden death. *Am Heart J* 58: 236, 1970.
- Ratshin R, Hunt D, Russell R & Rackle J. Prolonged Q T interval, paroxysmal rhythmias and convulsive syncope. *Ann Int Med* 75: 919, 1971.
- Romano D, Gemme G & Pongiglione R. Cardiac arrhythmias rare della pediatria Clinica (Bologna) 45: 656, 1963.
- Ward O C. A new family cardiac syndrome. *J Irish Med Assoc* 54: 103, 1964.
- Yanowitz F, Preston J B & Abildskov J A. Functional distribution of right and left stellate ganglia. Production of a unilateral electrocardiographic changes by unilateral stimulation of sympathetic tone. *Circ Res* 18: 416, 1966.

Carditis Associated with *Mycoplasma Pneumoniae* Infection

Antti Ponka

*From the Department of Virology, University of Helsinki, Helsinki, Finland*

**ABSTRACT** Among 560 patients with serologically confirmed *Mycoplasma pneumoniae* infection, 25 (4.5%) had carditis (19 perimyocarditis, 6 pericarditis). During the acute phase 9 patients required intensive care. After an average of 16 months follow up 11 patients with no previous signs of heart disease still had cardiac symptoms or signs. Thus carditis associated with *M. pneumoniae* infection is a serious disease having cardiac sequelae more often than has hitherto been supposed. The pathogenesis of the carditis associated with *M. pneumoniae* infection is discussed, including the possibility that in some cases elevated titre in the complement fixation test is specific. A summary is given of the 33 cases previously presented in the literature.

**Keywords:** *Mycoplasma pneumoniae*, pericarditis, perimyocarditis.

Acta Med Scand 206: 77-86, 1979.

Carditis played by *Mycoplasma pneumoniae* in the pathogenesis of respiratory infections is generally neglected and has been widely studied. Involvement of organ systems including the cardiovascular, gastrointestinal, central nervous, musculoskeletal, genitourinary systems and the blood is less well appreciated. Carditis has been considered a very rare complication of *M. pneumoniae* infection; only 33 cases have been presented so far in the literature (2, 14, 18-22, 27, 28, 30, 31, 33-36, 40, 41, 43).

The purpose of the present investigation was to define the clinical picture and occurrence of the cardiovascular manifestations associated with *M. pneumoniae* infections.

## PATIENTS

The basic series consisted of 560 patients treated during 77 in different hospitals in Helsinki who had had at a fourfold titre rise in the *M. pneumoniae* complement fixation test (CFT). Information remitted with sera for the main diagnosis was used to identify the patients with cardiac manifestations. 69 patients were found by this method.

The hospital records of these patients were examined and those were selected who had carditis for which no causal agent other than *M. pneumoniae* could be serologically and/or culturally suspected. The number of such patients was 25. Another group selected were the patients whose titre rise had not been associated with a respiratory infection at the time or during the previous month and who had acute ischaemic heart disease or carditis for which besides the *M. pneumoniae* infection, an alternative cause could be suggested. The number of such patients was 11.

## METHODS

*Diagnostic criteria of carditis*

The diagnosis of pericarditis was established if the patient had at least two of the following symptoms or findings: Specific electrocardiographic (ECG) abnormalities consisting of ST segment elevation without reciprocal depression, characteristic precordial chest pain, pericardial friction rub or pericardial effusion. The main criteria of perimyocarditis were ECG changes (transient ST-T abnormalities, arrhythmias and/or disturbances in conduction) for which no cause other than *M. pneumoniae* infection was found. In two patients the diagnosis was based solely on the changes in ECG; neither of them had any previous history of cardiac disorder. The others had in addition at least one of the following criteria: transient cardiac murmur, transient cardiac enlargement, transient cardiac failure in a patient under the age of 25 for which no other cause was found, or changes in echocardiography suggesting carditis.

*Serology*

Every patient had at least a fourfold titre rise in the *M. pneumoniae* CFT. Sera from all but one patient were tested for complement fixing antibodies to herpes simplex, cytomegalovirus, influenza A and B, parainfluenza, poliovirus, respiratory syncytial virus, measles and Coxsackie B5 viruses, ornithosis agent and toxoplasma. No diagnostic rises were found. Hepatitis B antigen was also negative in every patient, but was not examined in one. Most patients underwent even more comprehensive serological and bacteriological examinations.

A micromodification of the CF technique was used. The

**Abbreviations:** CFT=complement fixation test, ECG=electrocardiogram, MI=myocardial infarction.



and an unusually deformed T wave with varying amplitude the T wave may be positive negative or biphasic. A normal ECG does not eliminate the possibility of the syndrome because the Q T changes can be intermittent (3). If the syndrome is suspected repeated ECGs should be taken and possibly also an exercise ECG (12). It should be noted however that a prolonged Q T interval can be seen in connection with other conditions not related to the syndrome for example in myocardial necrosis or with certain stimulations of the autonomic nervous system (6).

A prolonged Q T interval can also be seen in connection with ingestion of certain drugs such as quinidine in connection with hypokalemia or hypocalcemia in connection with cerebrovascular accidents or after Adams Stokes attacks (1, 9). Q T changes related to the above conditions are however reversible. The cause of the heart symptom in the Q T syndrome is still unclear. In some cases primary damage to the myocardium has been suspected (7). Another theory is that an asymmetrical sympathetic stimulation of the myocardium occurs (16). With a prolonged Q T interval the refractory period is considerably longer in certain parts of the myocardium than in other parts. The difference in the length of the refractory period in different parts of the myocardium promotes the origin of ventricular fibrillation through the R on T phenomena (3).

The fact that the parents are cousins and that the syndrome occurs in only one generation strongly supports earlier observations that the syndromic cardiac syndrome has a recessive inheritance. The moderate prolongation of the Q T interval of unaffected members of the family (Fig. 3) may as Fraser et al. (2) postulated indicate that they are heterozygote carriers of the trait.

## REFERENCES

- 1 Burch G E, Meyers R & Abildskov J A. A new electrocardiographic pattern observed in cerebrovascular accidents. *Circulation* 9: 719, 1954.
- 2 Fraser G R, Froggatt P & Murphy T C. Aspects of the cardio-auditory syndrome of and Lange Nielsen (congenital deafness and electrocardiographic abnormalities). *Ann Hum Genet* 28: 133, 1964.
- 3 Furberg C & Hörnell H. Familial Q T prolongation and risk of sudden death. *Acta Paediatr Scand* 1975.
- 4 Gale G E, Bosman C K, Tucker R B, Barlow J B. Hereditary prolongation of Q T interval: study of two families. *Br Heart J* 33: 505, 1975.
- 5 Garza L A, Vick R L, Nora J J & McNamara D G. Hereditary Q T prolongation without deafness. *Circulation* 41: 39, 1970.
- 6 Han J, Garcia de Jalón P & Moe G K. A genetic effects of ventricular vulnerability. *Circulation* 34: 516, 1964.
- 7 James T N. An etiologic concept concerning obscure myocardial pathologies. *Prog Cardiovasc Dis* 6: 4, 1964.
- 8 Jervell A & Lange Nielsen F. Congenital deafness, functional heart disease with prolonged Q T interval and sudden death. *Am Heart J* 1957.
- 9 Johansson B W. Adams Stokes syndrome: view and follow up study of forty two cases. *Cardiol* 8: 76, 1961.
- 10 Johansson B W, Furberg C, Heinrich G J, Hörnell H, Johansson B W, Jörres Malmberg L & Voigt G. The long Q T interval. *Läkartidningen* 72: 4620, 1975.
- 11 Mathews E C, Blount A W Jr & Towne R R. Q T prolongation and ventricular arrhythmias and without deafness in the same family. *Am Heart J* 29: 702, 1972.
- 12 Philips J & Ichinose H. Clinical and pathologic studies in the hereditary syndrome of a prolonged Q T interval, syncopal spells and sudden death. *Am Heart J* 58: 236, 1970.
- 13 Ratshin R, Hunt D, Russell R & Rackle J. Interval prolongation, paroxysmal ventricular tachycardia and convulsive syncope. *Ann Intern Med* 75: 919, 1971.
- 14 Romano D, Gemme G & Pongiglione R. Cardiac rare dell'età pediatrica. *Clus (Bologna)* 45: 656, 1963.
- 15 Ward O C. A new family cardiac syndrome. *J Irish Med Assoc* 54: 103, 1964.
- 16 Yanowitz F, Preston J B & Abildskov J A. Functional distribution of right and left stimulation of the ventricles. Production of electrocardiographic changes by unilateral stimulation of sympathetic tone. *Circ Res* 18: 416, 1966.

Table III ECG changes in 19 patients with perimyocarditis associated with *M. pneumoniae* infection

	N
ECG changes only	5
ECG changes +	
1st degree AV block	3
1st degree AV block + ventricular ectopic beats	1
atrial fibrillation	2
atrial flutter with 2:1 and 4:1 conduction	1
ventricular ectopic beats	1
dyscardia + ventricular bigeminal ectopic beats	1
paroxysms of ventricular tachycardia	1
paroxysmal ventricular tachycardia	1
atrial fibrillation	1
atrial bigeminal ectopic beats	1
isolated ventricular ectopic beats	1

had radiologically verified pneumonia. In 8 of the 11 the onset of respiratory symptoms occurred during the week preceding the diagnosis of carditis. In 6 within 1-2 and in 3 within 2-4 weeks. The interval between the onset of respiratory symptoms and carditis was 11 days.

The main non respiratory symptoms are listed in Table II. Of the patients with pericarditis, one was completely free from cardiac symptoms and 5 had mild chest pains and a temperature of over 37°C. One patient with pericarditis had palpitations and dyspnoea. Of the patients with perimyocarditis, 11 had no cardiac symptoms. Sixteen patients had 9 chest pains, 6 dyspnoea and 4 palpitations. Six of the 25 patients, 7 had no cardiac symptoms and 9 were in good condition despite symptoms.

Table IV Manifestations of carditis

	N
Carditis	
without pericardial effusion	2
with pericardial effusion	4
Myocarditis	
with ECG changes only	2
with ECG changes and cardiac enlargement	5
with ECG changes and transient cardiac murmur	8
with ECG changes, transient murmur and cardiac enlargement	4
Total	25

Table V Cardiac sequelae in 23 patients after a mean follow up time of 16 months

	N	Age (y)
None	9	9 13 17 20 23 24 46 67 68
Cardiac failure for 1 y	1	1
Cardiac failure	3	57 62 66
Atrial fibrillation	3	26 30 49
Ventricular ectopic beats for 4 mo	1	39
Ventricular ectopic beats	2	29 49
1st degree AV block for 3 mo	1	20
1st degree AV block	2	32 44
Myocardial infarction 3 and 5 mo after perimyocarditis	1	25

symptoms. Nine patients were so severely ill that they required intensive care. Two patients required respirator treatment and one patient had temporarily a pacemaker because of bradycardia and ventricular ectopic beats. One patient was successfully resuscitated from ventricular fibrillation.

### Findings

Transient murmur was found on auscultation in 18 patients. In 12 this was friction rub. Two patients had both friction rub and other kind of transient murmur.

All patients with pericarditis had ST-T changes in the ECG. Two had transient atrial fibrillation. In one of them this returned to sinus rhythm after an episode of nodal tachycardia. The ECG changes in the patients with perimyocarditis are presented in Table III. Four patients had conduction disturbances, 6 cardiac arrhythmias and 5 ventricular ectopic beats.

Chest X-ray showed that 4 patients with pericarditis had pericardial effusion. In 2 the cardiac finding was radiologically normal. In the perimyocarditis group, 9 patients had transient cardiac enlargement. The findings are listed in Table IV.

Echocardiography was carried out in 4 patients. In one patient the finding was normal, one had pericardial effusion and 2 patients had a finding pointing to myocarditis.

### Laboratory findings

ESR was normal in 3 patients, 10-50 mm/h in 11 and over 50 mm/h in 11. The leucocyte count was nor-

Table VI Eleven patients with cardiac disease of miscellaneous aetiology with at least fourfold  $t_{11}$  pneumoniae CFT titres without simultaneous or preceding respiratory symptoms

Pat no	Age (y)	Sex	Diagnosis	M. pneumoniae CFT titre	Day of illness
1	1	♀	Hypovitaminosis B1 perimyocarditis	<8 16	3 25
2	13	♀	Systemic lupus erythematosus pericarditis	16 128	NK NK
3	43	♂	Uraemia pericarditis	8 64	10 21
4	45	♀	Bacterial endocarditis (Staphylococcus albus)	8 64	10 22
5	47	♂	Bacterial endocarditis ( $\alpha$ haemolytic streptococcus)	<8 32	NK NK
6	49	♂	MI	8 64	2 12
7	36	♂	MI	8 128	2 10
8	67	♂	MI	<8 32	15 26
9	63	♂	MI	8 128	5 15
10	52	♂	MI	8 32	1 10
11	47	♂	Arteriosclerotic heart disease cardiac failure	8 32	12 17

NK=not known

in 17 patients and 8 had leucocytosis of over  $1000/\text{mm}^3$ . The blood values of alanine amino transferase and aspartate aminotransferase were determined in 22 patients. Elevated levels were found in 12 more than half the cases usually both values were elevated. Slightly elevated serum creatinine levels were found in 5 patients, one of whom had acute transient glomerulonephritis with haematuria and proteinuria. Antistreptolysin O titre determined in 23 patients rose temporarily to 560 in one patient.

It has previously been suggested that in some cases of carditis raised titres in the CFT for M. pneumoniae could be non specific and that low titres in the CFT point to this (39). The maximal M. pneumoniae CFT titres of the patients with carditis were therefore compared with the titres of control patients with various manifestations of M. pneumoniae infection. The median of the maximal titres was higher in the carditis group than in the control group 74/24 and 57/87, respectively. However the difference between the groups was not statistically

significant ( $p>0.05$ ) owing to the small patients with carditis.

#### Antibiotic treatment

Eleven patients were given adequate treatment erythromycin, tetracycline or cline for at least a week. The others received antibiotics which are ineffective against M. pneumoniae or no antibiotic treatment at all. The mean of hospitalization in the groups with and without adequate antibiotic treatment was 26 and 12 days, respectively, and the number of patients with permanent cardiac sequelae 4 and 7. Thus, treatment with antibiotics known to be effective against M. pneumoniae neither shortened the duration of illness nor clearly diminished the number of sequelae—a fact which may be of significance in the evaluation of the pathogenesis of carditis with M. pneumoniae infection.

#### Follow up and cardiac sequelae

The average hospital stay was 24 days. All patients were invited to later check ups. 2 did not

VII Maximal *M. pneumoniae* CFT titres in patients with carditis associated with *M. pneumoniae* infection (A) carditis or acute ischaemic heart disease without respiratory symptoms and presumably of aetiology than *M. pneumoniae* infection (B) and various manifestations of *M. pneumoniae* infection

No.	Maximal titres/N						Median titres
	16	32	64	128	256	512	
25)	3	3	6	8	2	3	74.24
11)	1	4	3	3	0	0	37.12
963)	62	198	274	166	160	103	57.87

remaining 23 were followed up as out patients on an average of 16 months. None of the patients during the follow up period.

Only 2 of the patients in this study had had pre-existence of heart disease: cardiac failure and myocardial infarction respectively. Both recovered from the illness, regaining their previous condition. In all during the check ups 9 patients were in good condition and without symptoms or signs of heart disease.

Fourteen presented with cardiac sequelae (Table V) in 3 patients symptoms disappeared during the follow up. Thus cardiac damage persisted in a follow up period in 11 patients. Three patients—all of fairly advanced age, the youngest 57 old—developed cardiac failure. Atrial fibrillation persisted in 3 patients, ventricular ectopics in 2 and first degree AV block in 2. A 25 year old man with no previous history of cardiac disease developed myocardial infarction for the first time 10 months and for the second time 5 months after myocarditis.

No doubt has been raised before about the possible non specificity of *M. pneumoniae* CFT in association with heart complications (39). Attention was also focused on the patients who had acute myocardial tissue damage without any preceding or simultaneous respiratory infection that could explain the rise in titre. Eleven such patients were found (Table VI).

Five of the 11 patients had carditis with at least a fourfold rise in the *M. pneumoniae* CFT titre. In the aetiology of these cases, however, there turned out to be some other alternative. One patient had hypothyroidism, B1 one acute systemic lupus erythematosus and one exacerbation of uraemia. Two patients had bacterial endocarditis, one due to *Staphylococcus albus* and the other to *Streptococcus*.

group A. Five patients who had myocardial infarction (MI) were screened for antibodies because carditis had been suspected in the early stages of the illness. Lastly, one patient developed acute cardiac failure as a consequence of arteriosclerotic heart disease.

When comparing the maximal *M. pneumoniae* CFT titres of these 11 patients with the titres of the 25 patients with carditis presented above, one can see that the latter patients had higher titres (Table VII) (median 74.24 and 37.12). For these small groups the difference is not statistically significant. However, in the group of 11 patients the highest titre found was 128, while 5 (20%) of the 25 patients with carditis had titres higher than that.

## DISCUSSION

Carditis associated with *M. pneumoniae* infection is commonly thought to be a rare disease; only 33 cases have been published up to 1978 (Table VIII). Grayston et al. (20) in 1965 were the first to present a case of heart complication associated with *M. pneumoniae* infection: a 20-year-old woman with transient pericarditis. The first case report in which *M. pneumoniae* infection was serologically reliably demonstrated was presented in 1969 by Lambert who described a 50-year-old man with recurrent pericarditis (28). Since then 31 cases have been published of patients who had carditis associated with *M. pneumoniae* infection (11, 12, 14, 18, 19, 21, 22, 27, 30, 31, 33–36, 40, 41, 43). Of these 13 cases were presented as case reports. The diagnosis of *M. pneumoniae* was based in 2 cases on isolation and in 31 on CFT, 26 of them having at least a fourfold rise in titre.

The age of 30 patients presented in the literature is known—only 5 of them were younger than 20—

Table VIII Some aspects of carditis associated with *M. pneumoniae* infection summary of 13 described in the literature

Source	Age (y)	Sex	<i>M. pneumoniae</i> test	Respiratory diagnosis	ECG changes	Diagnosis
Grayston et al (20)	20	♀	Isolation	NK	NK	Pericarditis
Rosner et al (40)	18	♂	CFT 16-8	Pharyngitis	3rd degree AV block	Myocarditis
Hers (21)	NK	NK	CFT	NK	NK	Perimyocarditis
Lambert (28)	50	♂	CFT 0-128	-	Flattened or inverted T waves in leads aVL V 4-7	Recurrent perimyocarditis
Gerzen et al (19)	NK	NK	Rising titre in CFT	Pneumonia	NK	Myocarditis
	NK	NK	"Rising titre in CFT"	Pneumonia	NK	Myocarditis
Feizi et al (12)	30	♀	CFT 80-640	Pneumonia	Inverted T waves in leads III aVF and 1st degree AV block	Myocarditis
Fischer (14)	23	♀	CFT 30-480	Pneumonia	Inverted T waves in leads aVL V 2-6 and 1st degree AV block	Myocarditis
Lewes et al (30)	19	♀	CFT single convalescent titre ≥ 256	Pneumonia	Inverted T waves in leads V 4-6	Myocarditis
	27	♀	CFT single convalescent titre ≥ 256	Rhinitis	Flattened or inverted T waves in leads II, III aVF V 4-6 and coving of S-T segment in leads II III aVF	Myocarditis
Müller & Stelzner (35)	31	♀	CFT 40-160	Pneumonia	Inverted T waves in leads I II V 3-6 and depressed S-T segments in leads I II V 2-6	Myocarditis
Mårdh & Ursing (33)	15	♀	CFT 10-1280	Pneumonia	Transient inverted T waves	Myocarditis
Naftalin et al (36)	71	♂	Isolation from blood and pericardial exudate after death	Pneumonia	Episodes of atrial flutter and bundle branch block	Perimyocarditis
Fatih & Lerner (27)	20	♂	CFT single titre 128 (cold agglutinin titre 131072)	Pneumonia	Inverted T waves in leads II III aVF V 1-6	Perimyocarditis
Mackay et al (31)	48	♂	CFT 32-128	Pharyngitis and pleuritis	Inverted T waves in leads I aVL depressed S-T segment in aVL and ventricular ectopic beats	Myocarditis
De Vos et al (11)	30	♂	CFT 4-64	Pneumonia	Inverted T waves in all leads	Myocarditis
Stuckey et al (43)	37	♀	CFT <8-512	Pneumonia	Inverted T waves and depressed S-T segments in leads II III aVF	Pericarditis
Holt et al (22)	34	♂	CFT 1280-40	Pneumonia	Flattened T waves and S-T segment arching in leads II III aVF V 1-2	Myocarditis
Friedl et al (18)	1	♀	16-128	Upper respiratory tract infection	3rd degree AV block and right bundle branch block	Myocarditis
Maresh et al (34)	49	♀	CFT negative-64	Pneumonia	Q waves in leads I II III aVF and ST T changes in I aVR aVL V 1-6	Myocarditis
Sands et al (41)	54	♂	CFT >8-32	Pneumonia	Epicardial injury current	Perimyocarditis
	44	♂	CFT 32-256	Pneumonia	Epicardial injury current	Pericarditis
	75	♂	CFT 8-64	Pneumonia	Epicardial injury current	Pericarditis
	60	♂	CFT 8-32	Pneumonia	Epicardial injury current	Pericarditis
	49	♂	CFT 16-1024	Pneumonia	Non-specific ST T abnormality	Perimyocarditis

## VIII (Cont.)

	Age (y)	Sex	M. pneumoniae test	Respiratory diagnosis	ECG changes	Diagnosis
	54	♂	CFT 8-256	Pneumonia	Non specific ST T abnormality	Perimyocarditis
(41)	18	♂	CFT 8-32	-	Non specific ST T abnormality	Perimyocarditis
	52	♀	CFT <8-16	-	Non specific ST T abnormality	Pericarditis
	38	♂	CFT <8-16	-	Non specific ST T abnormality	Perimyocarditis
	27	♂	CFT <8-16	-	Epicardial injury current	Pericarditis
	30	♀	CFT <8-64	-	Epicardial injury current	Pericarditis
	35	♂	CFT <8-32	-	Epicardial injury current	Pericarditis
	65	♂	CFT 256-256	-	Non specific ST T abnormality	Pericarditis

not known

average age being 37. The average age of the first patients is almost identical. 38. The patients with arditis are therefore older than those in general with *M. pneumoniae* infection who usually are in the ages of 5 and 20 years. The sex distribution of 30 of the previously presented patients is 12 women and 18 men. In the present study 12 respectively.

Of the 33 patients presented in the literature 25 respiratory infection in the recent case history associated with carditis. 19 had pneumonia and 6 other respiratory tract infection. In one with pleurisy for 2 patients no specific diagnosis was given. 7 patients had no history of respiratory infection. In the present study the respiratory diagnoses and their relative frequencies are quite comparable to those presented previously.

9 of the patients presented in the literature the finding is known. 26 had ST T changes. 2 of them had first degree AV block and one ventricular premature beats. One patient had third degree AV block alone and one with right bundle branch block. One patient had episodes of atrial flutter with left bundle branch block.

Of the third or 11 of the patients presented previously had pericarditis, the others perimyocarditis or myocarditis. The carditis was fatal in only one. In this patient *M. pneumoniae* was isolated at autopsy from a blood sample from the heart and the pericardial exudate (36). One patient was with a permanent third degree AV block (18). In a series of 13 patients of Sands et al. (41) follow-up was continued for an average of 47 months.

During this period 2 patients died from causes not connected with the *M. pneumoniae* carditis. Cardiac symptoms of unknown quality persisted in 3 and 8

had no cardiac symptoms by the end of the follow-up period.

It has previously been believed that carditis is a rare complication of serologically confirmed *M. pneumoniae* infection. Only sporadic cases had been published until Sands et al. diagnosed 13 (9.2%) cases of carditis in a series of 141 patients with serologically verified *M. pneumoniae* infection. In the present series of 560 patients with serologically confirmed *M. pneumoniae* infection 25 (4.5%) had carditis. This high frequency may partly be explained by the fact that the Helsinki University Central Hospital receives selectively the more difficult cases from the provinces; the real frequency is lower.

Carditis associated with *M. pneumoniae* infection occurs in all seasons of the year, as do *M. pneumoniae* infections in general. This complication was found every year of the study except in 1977. When the annual numbers of carditis cases were compared with the numbers to be expected from the total number of *M. pneumoniae* infections, no statistically significant difference could be seen.

Clinically carditis associated with *M. pneumoniae* infection proved to be a serious illness. 9 of the 25 patients required intensive care in the acute phase. Five patients had dangerous frequent ventricular ectopic beats, one ventricular fibrillation and one episode of ventricular tachycardia. Two patients received respirator treatment. In Sands' series of 13 patients the results were fairly similar: 6 patients were classified as mildly, one moderately and 6 critically ill. The cardiac sequelae in the present study were more frequent, however, than has been previously described. At the end of the follow-up period of 16 months on average, 10 of the 23

patients had cardiac damage none of them had had previous cardiac disease. Moreover one patient a man of 25 had one episode of MI 3 months and another 5 months after recuperating from perimyocarditis.

The pathogenesis of the carditis associated with *M. pneumoniae* infection has not been elucidated. In theory it is even conceivable that *M. pneumoniae* has no part in the aetiology of these cardiac manifestations. The following possibilities exist:

A. The heart disorder in question is caused by *M. pneumoniae* directly or indirectly.

1. By direct invasion of *M. pneumoniae* into the heart. This could occur through the lymphatic vessels connecting the throat and tonsils with the heart (1) via the circulatory system (36) or from the lower respiratory tract per continuitatem.

2. By an autoimmune mechanism. *M. pneumoniae* infection may cause such a change in some component of the heart tissue that an autoimmune response is produced and this causes damage to cardiac tissue. On the other hand it is possible that the antibody is produced primarily against the *M. pneumoniae* antigen but owing to common characteristics of some component of cardiac tissue and *M. pneumoniae* lipid antigen a cross reaction is produced against the cardiac tissue. In 1943 Thomas et al. (44) showed that the cardiac tissue of beef had an antigen which reacted positively with convalescent sera from patients with primary atypical pneumonia which is nowadays known to be most commonly caused by *M. pneumoniae* so this may have antigen characteristics in common with heart tissue.

A similar autoimmune mechanism has been considered as one pathogenetic possibility in cases of pancreatitis in which *M. pneumoniae* CFT titres have been elevated (29). Biberfeld (3) showed that brain tissue and *M. pneumoniae* lipid antigen have traits in common so autoimmune phenomena may play a part also in the pathogenesis of central nervous system complications of *M. pneumoniae* infection.

Brunner et al. (5, 6) and Fernald et al. (13) have suggested that the pneumonia due to *M. pneumoniae* may be an immunopathological disease its severity depending on earlier sensitization by one or more silent infections. It is also possible that the non respiratory manifestations of serologically confirmed *M. pneumoniae* infection such as carditis, arthritis and central nervous system infections are

caused by an immunological mechanism. The pathogenesis of these could be similar to the related rheumatic fever. In this connection it is interesting to note that *M. pneumoniae* and *Coccidiosis* group A have antigenic properties in common. Brunner et al. (6) have shown that immunoprecipitating antibodies to *M. pneumoniae* were blocked by lipids from selected *Streptococcus* group A and *Staphylococcus*.

3. An increased tendency for blood coagulation and intravascular thrombosis has been noted in association with *M. pneumoniae* infections (1, 37, 38, 42). Possibly some part of the heart manifestations associated with *M. pneumoniae* can be explained on the basis of microthromboses of the coronary arteries. It is interesting that in a study of 5 MI patients who had elevated *M. pneumoniae* titres although no respiratory manifestations were suspected in the early phases of the disease having carditis.

B. Alternatively the carditis is not made due to *M. pneumoniae* infection the rise in *M. pneumoniae* can be non specific or it can have a double infection.

1. *Mycoplasma* other than *M. pneumoniae* may be the cause of the infection and there is a body cross reaction and a false positive result even though so far no *mycoplasma* species other than *M. pneumoniae* is known to be a human pathogen.

2. Another agent such as a virus or an unknown agent may primarily cause damage to cardiac tissue and change some component of the heart tissue in a way that an autoimmune reaction is produced. Since cardiac tissue may have antigen properties in common with the *M. pneumoniae* lipid antigen an *M. pneumoniae* CFT then gives a false result.

3. A further possibility is a double infection with subclinical or respiratory *M. pneumoniae* and simultaneous carditis caused by another agent.

In this series of 25 carditis cases the seasonal and annual distribution and the approximately equally high maximal titres in CFT for other *M. pneumoniae* infections point to a significant aetiological role for *M. pneumoniae*. This conclusion is supported by the case described by Viret et al. (36) in which *M. pneumoniae* was isolated from the pericardial exudate and blood.

The carditis associated with *M. pneumoniae*

is not necessarily always due to one and the same mechanism. More than one of the possibilities mentioned above may play a role in the pathogenesis. This view is supported by the observation that in the patients with carditis more or less coincided with the respiratory symptoms while in others it developed more than 2 weeks after they commenced. In some cases no respiratory symptoms were observed in these infections may have been subclinical.

The significance should then be attributed to the fact that the *M. pneumoniae* titres of the 11 patients with heart disease presumably caused by some other than *M. pneumoniae* and who did not suffer with any signs of a respiratory infection? It is probable that these patients did have a subclinical *M. pneumoniae* infection. Another possibility is that when cardiac tissue is damaged in some way an immune response is produced leading to a reaction and a false positive result in *M. pneumoniae* CFT as described above. Non-specificity of the elevated titres is supported by the observation that the maximal *M. pneumoniae* titres were in this group of 11 patients than in the group of patients with carditis. The 5 MI cases among the 11 patients are those in whom *M. pneumoniae* is thought to have played a causal role since a tendency to blood coagulation and intravascular calcification has been observed in *M. pneumoniae* infections.

Reactions due to *M. pneumoniae* are not uncommon accounting for 7-27% of all cases of pneumonia (16, 17, 20, 24, 25, 39). In addition more than pneumonia are the other types of respiratory involvement caused by *M. pneumoniae* (14, 19, 15). Since according to this investigation as many as a complication in as many as 4.5% of serologically confirmed *M. pneumoniae* infection it is reasonable to examine the ECGs of patients treated in hospital for respiratory infections for *M. pneumoniae* aetiology is present or suspected. Further the *M. pneumoniae* CFT can be recommended as a routine method for examining patients with carditis of unknown aetiology.

#### REFERENCES

Andrushin J N Some materials to anatomical substantiation of spread of infection from tonsils and adenoids to heart. *Arkh Anat* 56 45 1969  
 Balassanian N & Robbins F C *Mycoplasma pneumoniae* infection in families. *N Engl J Med* 277 719 1967

- 3 Biberfeld G Antibodies to brain and other tissues in cases of *Mycoplasma pneumoniae* infection. *Clin Exp Immunol* 8 319 1971
- 4 — Immunological, epidemiological and ultrastructural studies of *Mycoplasma pneumoniae*. p 14 Tryck en Balder Stockholm 1971
- 5 Brunner H Horswood R & Chanock R M More sensitive methods for detection of antibody to *Mycoplasma pneumoniae*. *J Infect Dis (Suppl)* 127 52 1973
- 6 Brunner H Prescott B Greenberg H James W D Horswood R & Chanock R M Unexpectedly high frequency of antibody to *Mycoplasma pneumoniae* in human sera as measured by sensitive techniques. *J Infect Dis* 135 524 1977
- 7 Campbell T A Strong P S Grier G S & Lietz R J Primary atypical pneumonia. *JAMA* 122 722 1943
- 8 Chanock R M Fox H James W D Gutekunst R R White R J & Senterfit L B Epidemiology of *Mycoplasma pneumoniae* infection in military recruits. *Ann NY Acad Sci* 143 484 1967
- 9 Couch R B Cate T R & Chanock R M Infection with artificially propagated Eaton agent. *JAMA* 187 442 1964
- 10 De Vos M van Nimmen L & Baele G Disseminated intravascular coagulation during a fatal *Mycoplasma pneumoniae* infection. *Acta Haematol* 52 120 1974
- 11 De Vos M van der Straeten M & Druyts E Myocarditis and severe bilateral bronchopneumonia caused by *Mycoplasma pneumoniae*. *Infection (Suppl)* 1 60 1976
- 12 Feizi O Grubb C Skinner J I Constantinidou M & Hendersson W G Primary atypical pneumonia due to *Mycoplasma pneumoniae* complicated by haemorrhagic pleural effusion, haemolytic anaemia and myocarditis. *Br J Clin Pract* 27 99 1973
- 13 Fernald G W Collier A M & Clyde W A Respiratory tract infection due to *Mycoplasma pneumoniae* in infants and children. *Pediatrics* 55 327 1975
- 14 Fisher G A propos d'un cas de pneumopathie à *Mycoplasma pneumoniae* résidant en un complice. *Rev Med Suisse Romande* 93 979 1973
- 15 Foy H M, Kenny G E, McMahon R, Mansy A & Grayston J T *Mycoplasma pneumoniae* in the community. *Am J Epidemiol* 93 55 1971
- 16 Foy H M Kenny G E McMahon R Mansy A & Grayston J T *Mycoplasma pneumoniae* pneumonia in an urban area. Five years of surveillance. *JAMA* 214 1666 1970
- 17 Franssen H Clinical and laboratory studies on the role of viruses, bacteria and bedsonia in acute respiratory illness. *Scand J Infect Dis (Suppl)* 1 17 1970
- 18 Friedl B Renevey F & Rouge J C Complete heart block in a young child presumably due to *Mycoplasma pneumoniae* myocarditis. *Acta Paediatr Scand* 66 385 1977
- 19 Gerzen P Granath A Holmgren B & Zetterqvist S Acute myocarditis. A follow up study. *Br Heart J* 34 575 1972
- 20 Grayston J T Alexander E R Kenny G E



- Clarke E R Fremont J C & MacColl W A Mycoplasma pneumoniae infections JAMA 191 97 1965
- 21 Hers J F P Clinical aspects of infection with Mycoplasma pneumoniae Proc R Soc Med 61 1325 1968
- 22 Holt S Charles R G Khan M M & Epstein E J Polyradiculoneuritis and Mycoplasma pneumoniae infection Postgrad Med J 53 416 1977
- 23 Jansson E Preparation of complement fixing antigen for routine use in diagnosis of Eaton pneumonia J Clin Pathol 17 458 1964
- 24 Jansson E Wager O Stenstrom R Klemola E & Forsell P Studies on Eaton PLO pneumonia Br Med J 1 142 1964
- 25 Jones M C Mycoplasma infections of the respiratory tract Br Thorac Tuberc Assoc Rev 1 1 1971
- 26 Kenny G E & Grayston J T Eaton pleuropneumonia like organism complement fixing antigen Extraction with organic solvents J Immunol 95 19 1965
- 27 Khatib M R & Lerner A M Myocarditis in Mycoplasma pneumoniae pneumonia Occurrence with hemolytic anemia and extraordinary titers of cold isohemagglutinins JAMA 231 493 1975
- 28 Lambert H P Infections caused by Mycoplasma pneumoniae Br J Dis Chest 63 71 1969
- 29 Leinikki P Pantzar P & Tykkä H Antibody response in patients with acute pancreatitis to Mycoplasma pneumoniae Scand J Gastroenterol 8 631 1973
- 30 Lewes D Rainford D J & Lane W F Symptomless myocarditis and myalgia in viral and Mycoplasma pneumoniae infections Br Heart J 36 924 1974
- 31 Mackay A D Watt J B & Jones G R Myocarditis associated with Mycoplasma pneumoniae infection Practitioner 214 390 1975
- 32 Maisel J C Babbitt L H & John T J Fatal Mycoplasma pneumoniae infection with isolation of organisms from lung JAMA 202 287 1967
- 33 Mårdh P A & Ursing B The occurrence of acute pancreatitis in Mycoplasma pneumoniae Scand J Infect Dis 6 167 1974
- 34 Maresh H Klimek J J & Quintiliani R Renal dysfunction and hemolytic anemia in a child with Mycoplasma pneumoniae infection JAMA 238 410 1977
- 35 Muller H & Stelzner A Zur Frage der Pathogenität nach Mycoplasma pneumoniae Infektion Zentr Bl Bakt 29 164 1974
- 36 Naftalin J M Wellisch G Kahana Z D Mycoplasma pneumoniae septicemia JAMA 228 565 1974
- 37 Nilsson J M Rausing A Denneberg T Jørgensen P Intravascular coagulation and its failure in a child with Mycoplasma pneumoniae Med Scand 189 359 1971
- 38 Noran H H & Baker A B The ceroid system in pneumonia II A pathologic study J Pathol 22 579 1946
- 39 Ponka A Clinical and laboratory manifestations in patients with serological evidence of Mycoplasma pneumoniae infection Scand J Infect Dis 6 178 1974
- 40 Rosner P Eichenberger G Ferrero C Nik O Bloc auriculo-ventriculaire compliqué de Mycoplasma pneumoniae Sch Wehenschr 40 1343 1966
- 41 Sands M J Satz J E Turner W E A Pericarditis and perimyocarditis associated with active Mycoplasma pneumoniae infection JAMA 238 544 1977
- 42 Sterner G & Biberfeld G Central nervous system complications of Mycoplasma pneumoniae Scand J Infect Dis 1 203 1969
- 43 Stuckey J Wahlqvist M L Peak H J J Pericarditis during infection with Mycoplasma pneumoniae Med J Aust 2 643 1976
- 44 Thomas L Curnen E C Mirick G S E & Horsfall F L Complement fixable antigens in primary atypical pneumonia Soc Exp Biol Med 52 121 1943

# A Controlled Study of Early Discharge after Uncomplicated Myocardial Infarction

Gosta Ahlmark Greger Ahlberg Helge Sætre  
Ingegerd Haglund and Magnus Korsgren

*From the Department of Medicine Falu Hospital Falun Sweden*

**ABSTRACT** Out of 383 myocardial infarction (MI) patients aged below 70 years 252 (66%) were judged on the third day in hospital to have had uncomplicated infarctions. These patients were allocated at random to two groups one of which was given treatment for 8 days and the other for 15 days. No significant differences in mortality, morbidity or inability for work could be detected during the 12-month period of follow up. The findings thus confirm previous conclusions that early discharge from hospital after uncomplicated MI is not associated with greater risk for the patient than later discharge.

**Keywords:** myocardial infarction early discharge hospitalization

Acta Med Scand 206 87 1979

The management of acute myocardial infarction (MI) was formerly characterized by prolonged immobilization of the patient and long periods of hospitalization. During the 1950's however it was shown that the need of bed rest could be substantially shortened without increasing the risk of complications (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100).

During the last decade the period of hospitalization has been further cut down to about two weeks for patients with uncomplicated MI without an increase in mortality (1, 8, 11, 22, 24). Several investigations indicate that the period of hospitalization can be further reduced (2, 5, 7, 16, 17, 23, 24) but there are few controlled studies (9). The aim of this prospective randomized controlled investigation was to study whether patients with uncomplicated MI could be discharged from hospital after eight days treatment instead of 15 days without an increase in mortality morbidity or inability for work.

## PATIENTS AND METHODS

The study was performed at Falu Hospital which has a catchment area comprising industrial towns small towns and villages and rural areas with a population of 128 000. The study comprised patients treated at the Coronary Care Unit (CCU) for acute myocardial infarction with onset less than 48 hours before admission to hospital. Patients who had sustained MI during the preceding three months or who were above 70 years of age were excluded. The diagnosis of MI was based on conventional criteria (27). The patients were kept under observation in the CCU for three days after which the survivors were assessed by one of the physicians participating in the study. Patients with any of the following contraindications after 72 hours in hospital were excluded: 1) Maximal serum aspartic aminotransferase (SASAT)  $\geq 5.5 \mu\text{kat/l}$  (S-GOT  $\geq 300 \text{ IU}$ ); 2) Persistent arrhythmias despite treatment; second degree and complete AV block multifocal ventricular extrasystoles supraventricular tachycardia  $\geq 110/\text{min}$ ; 3) Chest pain requiring continuous treatment with analgesics; 4) Heart failure in spite of treatment; 5) Cardiogenic shock; 6) Pericarditis with a temperature of  $\geq 38.5^\circ\text{C}$ . The remaining patients were randomly allocated to two groups with different mobilization programmes.

After 72 hours the patients were transferred to a second coronary CCU where they were monitored on an oscilloscope for a further four days. One group of patients were mobilized on the fourth and fifth days of treatment respectively on the fourth and fifth days of treatment. They were given their clothes and allowed to move about the ward from the sixth day and were discharged after the eighth day of treatment (the 8-day group). The patients in the other group were mobilized gradually after the third day and allowed to get out of bed from the 12 day and discharged 15 days after admission (the 15-day group). The patients in either group who were unable to follow the mobilization programme were excluded from the study. In addition the patients were assessed with respect to the contraindications listed above and any new complicating disease (bronchial pneumonia thrombosis embolism) on

**Abbreviations:** MI = myocardial infarction CCU = coronary care unit SASAT = serum aspartic aminotransferase

Table I Main reasons for exclusion of patients from the study after the third day of treatment in each group

	8-day group (n=21)	15-day group (n=24)
Angina pectoris	9	7
Arrhythmia	2	5
Heart failure	2	3
Thrombosis	1	1
Postmyocardial infarction syndrome/bronchial pneumonia	2	1
Tiredness/inability to cooperate	5	7

Table III Number of reinfarctions and admissions to hospital during the 3 months follow-up in each group

	8-day group	15-day group
Fatal reinfarction	5	2
Non-fatal reinfarction	6	3
Other hospital treatment	4	9
Angina pectoris/suspected infarction*	2	1
Arrhythmia	1	1
Cardiac decompensation	1	6

\* Chest pain and unspecific S-T or T wave abnormalities and normal transaminases or characteristic enzyme elevation within the normal range

the eighth day and were excluded when appropriate. At discharge all patients were given the same rehabilitation advice and smokers were advised to give up smoking.

During the three month follow-up the patients were controlled at the department's outpatient clinic one week after discharge and six and 12 weeks after onset of infarction. All deaths, reinfarctions and periods of hospital treatment due to cardiac causes were also recorded.

## RESULTS

During the period Sept 1 1975-Jan 31 1978 383 patients were treated for MI at the CCU. Forty-eight patients died and 83 were excluded owing to contraindications during the three days. 57 patients had max S-ASAT  $\geq 5.5 \mu\text{kat/l}$ , 34 persistent arrhythmias, 14 severe chest pain, 11 heart failure with or without cardiogenic shock and 3 pericarditis.

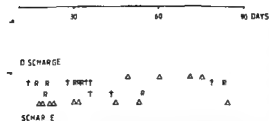
Table II Sex, age, number of smokers, occurrence of previous diseases, cardiac volume and maximal S-ASAT during hospital treatment of the patients in each group

	8-day group (n=106)	15-day group (n=100)
Women (%)	24	18
Mean age (y)	60.7	61.9
Smokers (%)	42	50
Previous diseases (%)		
MI	16	22
Diabetes mellitus	13	4
Hypertension	24	29
Cardiac volume ( $\text{ml/m}^2$ )	504	511
S-ASAT ( $\mu\text{kat/l}$ )	1.9	2.0

with a high temperature. Of the remaining 21 patients, 21% of whom were women, 128 were allocated to the 8-day group and 124 to the 15-day group. Forty-five patients were excluded from the study after the third day (Table I). There were no statistically significant differences between the groups in this respect. In the 8-day group, one 61-year-old man died from a myocardial infarction and cardiogenic shock with papillary muscle rupture almost four days after admission. 24 patients in the 15-day group were excluded owing to complications: 20 (83%) were withdrawn during the first eight days and two other two during the ninth day. Altogether 69 patients were excluded from the study because of complications and 13 (10.2%) of them died in hospital. Only one (0.5%) of the 207 patients who had no complications died. Twenty-two patients with S-ASAT max  $\geq 5.5 \mu\text{kat/l}$  did not fulfil any of the other criteria for exclusion and were excluded solely because of the transaminase elevation. Of these 29 patients, four (14%) died and two suffered reinfarction during follow-up.

Thus, 106 patients were discharged after 8 days and 100 patients after 15 days. Details of sex, age, previous diseases and certain variables during hospital treatment for these two groups are given in Table II. At the time of discharge there was no statistically significant difference between the two groups with respect to treatment with diuretics, antiarrhythmics or  $\beta$ -blocking drugs.

During the period of follow-up, five patients (4.7%) died due to reinfarction in the 8-day group and two (2%) in the 15-day group (Table III).



Deaths (†) non fatal reinfarctions (R) duration of treatment (Δ) and other periods of hospital treatment during the follow up period (Δ)

ven patients who died had been readmitted in hospital after several days. One patient in the 8 day group suffered reinfarction six days after discharge and died shortly after readmission. The difference is not statistically significant. The 252 individuals allocated to the two groups had thus not required additional hospital treatment three months after onset of infarction. In the 8-day group 48% of the patients and in the 15-day group 47% reported symptoms of decompensation. Twenty per cent and 23% respectively suffered from dyspnoea on exertion and 2% had clinical decompensation.

The 206 patients discharged alive 54% in the 8-day group and 47% in the 15-day group were still alive at the time of onset of infarction. Within three months 65% and 49% respectively were able to resume work in the same or a lighter occupation. The patients with uncomplicated infarction 18% had diabetes mellitus compared to 23 (18%) patients excluded because of complications. One of the 18 diabetics belonged to the 8-day group and one of these 14 patients died and two suffered non fatal reinfarctions during the follow up period. One of the four diabetics in the 15-day group suffered reinfarction later.

## DISCUSSION

There is still some uncertainty as to the optimal length of hospital treatment and immobilization in so-called uncomplicated MI. It has been suggested that rapid mobilization might interfere with consolidation of the infarcted myocardium and increase the size of the infarct thereby increasing the risk of rupture of the ventricle (15) and development of ventricular aneurysm (19, 20). Furthermore arterial hypoxia in the acute phase of infarction might also increase the risk of reinfarction and arrhythmia. Several studies during the last decade have contradicted this hypothesis however (8, 11, 25). A longer period of hospital treatment might enable malignant arrhythmias to be detected and treated thus reducing sudden deaths. These conditions usually occur early in the course of infarction however and the occurrence of life threatening complications that are amenable to treatment is low after the first week of treatment (7).

More rapid mobilization might reduce the risk of thrombosis, embolism and pulmonary complications. Many authors have pointed out the psychological advantages of both a short period of immobilization and a short stay in hospital (14, 24). This may lead to more rapid rehabilitation and possibly a more rapid return to work. A shorter period of hospitalization also reduces the demand for hospital beds and thus probably entails major economic gains (16).

At present there are no reliable criteria for predicting after 2-3 days treatment whether or not an infarction will have an uncomplicated course. Different laboratory variables during the first days have been used to identify patients with extensive myocardial damage and/or a high risk of arrhythmia. Several indices for judging the long term prognosis after MI have been constructed (10, 21, 26). These indices have been fairly reliable for predicting cardiovascular death but not non fatal reinfarction.

Sinus tachycardia during the first day of treatment, persistent ST segment elevation, certain ventricular arrhythmias, second degree and complete AV block and chest pain during the first week in hospital have been used as prognostic variables in several studies concerning early discharge (2, 5, 27). In other studies patients with persistent cardiac decompensation (7, 9, 11, 18), hypotension (16, 17, 24), atrial tachycardia (17, 22) or cardiac enlarge-

ment (6-22) have been considered to run an increased risk of complications.

Similar exclusion criteria were applied in this study. Like Wilson and Pantridge (28) we excluded patients with high concentrations of S-ASAT, as the degree of enzyme elevation is considered to constitute a measure of myocardial damage (4, 13). We also considered it unlikely that patients with pericarditis pain at a high temperature during the third day of treatment would be able to follow the mobilization programme and these patients were therefore also excluded. Of the 14 patients who died in hospital after the third day of treatment, 13 (93%) had been excluded from the study, so that our criteria identified patients at risk with a rather high degree of accuracy.

After three days of treatment, three quarters of the patients were considered to have an uncomplicated infarction. Additional patients were excluded during the following days, however, mainly because of angina pectoris and tiredness. Thus, 62% could be discharged in accordance with the original plans. In previous studies with 7-9 days' hospital treatment, the corresponding proportion of uncomplicated infarctions has varied between 49 and 76% (5, 7, 9). One patient in the 8-day group died on the fourth day and it is difficult to judge whether or not this death could have been prevented by a longer period of bed rest.

The distribution by age and sex and the incidence of so-called risk factors for MI—number of previous infarctions, hypertension and smoking—did not differ between the 8-day and 15-day groups. Diabetics were overrepresented in the 8-day group, however. There was no difference with respect to treatment with digitalis, diuretics or other antiarrhythmic drugs between the two groups at the time of discharge or during follow-up.

Altogether seven patients (3.4%) died during the first three months, all from reinfarction, which is in fairly good agreement with mortality figures in other studies (2, 9). The patient in the 8-day group who died six days after discharge might have been saved if he had been kept in hospital. Of the 22 patients (10.7%) who were readmitted to hospital and survived, 10 belonged to the 8-day and 12 to the 15-day group. Six and three of these patients, respectively, had verified reinfarctions, whereas the remainder were mainly given the diagnosis of suspected infarction/angina pectoris. The shorter period of hospital treatment thus did not increase

the number of readmissions during follow-up. A statistically significant difference was found in the number of subjective cardiac symptoms, i.e. angina pectoris and dyspnoea. This finding is further supported by the fact that about the same number of individuals in both groups who had been working at the time of onset of infarction were able to return to work within three months, in agreement with the report of Tucker et al. (25).

Diabetic patients who sustain MI have been considered to need longer periods in hospital and the poorer long-term prognosis (7). This is also found in our study. The number of patients is too small, however, to permit an assessment of whether or not a longer period of hospital treatment would improve the prognosis for these patients.

To summarize, we have not been able to detect any significant differences in mortality, morbidity or capacity for work in patients with uncomplicated MI who were discharged after 8 days compared with those kept in hospital for 15 days. Patients who had not had MI during the preceding three months and who were more than 70 years of age or had other defined complications during their stay in hospital were excluded from the study. With the criteria applied, a low-risk group among the infarction patients could be identified. Whether diabetics should be judged otherwise in this respect is uncertain.

We have started mobilizing the patients on the third day, but this can probably be done earlier (14, 24). During the final part of the stay in hospital, great attention should be paid to the patient's subjective condition and symptoms such as tiredness, an abnormal reaction to light physical exertion, a total period of eight or nine days' hospital treatment would seem to be appropriate in most cases of uncomplicated myocardial infarction. The patient's hospital stay should be individualized, however, and the patient's domestic situation should be taken into consideration, so that early discharge is a first step in a successful rehabilitation and so in a preventive programme.

## REFERENCES

1. Adgey AAJ. Prognosis after early discharge from hospital of patients with myocardial infarction. *Heart J* 31: 750, 1969.
2. Boyle A, Barber J, M. Walsh M, J. Shrivastava G & Chaturvedi N. C. Early mobilization





# Comparison of Streptokinase with Heparin Late Results in the Treatment of Deep Venous Thrombosis

Lilian Johansson Goran Nylander Ulla Hedner and  
Inga Marie Nilsson

*From the Coagulation Laboratory and the Department of Roentgenology University of Lund  
Malmö General Hospital Malmö Sweden*

**ABSTRACT** Nineteen cases were reinvestigated 8-18 years after treatment with SK or heparin. Judging from personal interviews, foot volumetry and ography, treatment with SK appears to be more effective since it was less often followed by late postthrombotic changes.

**KEY WORDS:** streptokinase, heparin, venous thrombosis. *Acta Med Scand* 206: 93-1979.

The treatment of acute deep venous thrombosis (DVT) with streptokinase (SK) is used in order to dissolve the thrombus and preserve the valves of the venous system and thereby to prevent the development of the postthrombotic syndrome (4, 11). It is still debatable whether SK is a more effective drug than heparin. Only four prospective randomized comparative investigations of the two drugs in altogether 117 patients are on record (5, 18, 23). Judging from the phlebograms, the thrombus promptly disappeared in only 3 (5%) of 7 patients given heparin compared with 21 (60%) of those 35 given SK. It is, however, known that several years may elapse before appearance of sequelae (2). Documentation of the long term beneficial effect of SK therefore requires a long follow up, but only few really long-term follow-up studies of such patients are available (8, 14). Data also holds for studies of SK versus other drugs (9, 15, 23). Between 1963 and 1969 Robertson et al. (17, 18) treated 57 patients (3 treated on 2 occasions) in a prospective randomized series. The purpose of the present investigation was to re-examine these patients with regard to postthrombotic sequelae after SK or heparin treatment.

## STUDY POPULATION

Robertson's three coded series of altogether 57 patients with acute DVT had been treated with SK or heparin. All the patients had had symptoms for at most 96 hours before treatment. The doses and duration of treatment are given in Table I.

In series I (20 treatments, 19 cases) the diagnosis had not been verified phlebographically in the first 9 patients who were therefore not included in the present series. Of the remaining 11 cases, one was excluded because he had had thrombosis of a subclavian vein. One patient had been treated twice, on the first occasion with heparin and on the second with SK. He had died several years after the treatments. Another 2 patients treated with heparin and one treated with SK had also died. Thus 5 patients were left for the present investigation: 2 treated with heparin and 3 with SK.

In series II (16 treatments, 16 cases) 6 of the 8 patients treated with heparin and 2 SK treated patients had died. Two could not take part because of advanced age and associated difficulties. One patient treated with SK had developed severe arterial insufficiency in both legs and had to be omitted. This left 5 patients for the present study: 2 treated with heparin and 3 with SK.

In series III (16 treatments, 14 cases) one patient had been treated twice for DVT on the same leg, first with heparin and due to recurrence 2 weeks later with SK. One patient was not included because his DVT was confined to the calf veins only. Three of the heparin treated and two of the SK treated patients had died. One patient had emigrated and one could not be traced. Two cases treated with heparin and 4 with SK plus the patient first treated with heparin and later with SK were thus available for the present study.

In the supplementary series, in which 8 patients had been given SK, 4 had died and one had emigrated. This left 3 patients for reinvestigation.

**Abbreviations:** DVT=deep venous thrombosis; SK=streptokinase; EV=volume expelled;  $EV_{rel}$ =EV relative to foot volume;  $\dot{Q}$ =rapid phase of refilling flow after exercise;  $\dot{Q}_{rel}$ =flow relative to foot volume;  $Q/\dot{EV}_{rel}$ =time factor;  $t_{1/2}$ =half-life;  $t_{1/2}$ =half-life.



Table I Administration of SK number of treatments with SK or heparin and number of reinvestigation

	Series I (treated in 1963-65)	Series II (treated in 1965-67)	Series III (treated in 1967-68)	Supplemental (treated in 1968)
Initial dose	1x1 i.d. for 30 min+ 1x1 i.d. for 60 min	2x1 i.d. for 90 min	2x1 i.d. for 90 min	500 000 IU of SK for 60 min
Maintenance dose of SK (IU/h)	50 000	100 000	100 000	100 000
Total duration of treatment (h)	12	24	72	72
No. of treatments				
SK	12	8	8	8
Heparin	18	8	8	8
No. of reinvestigations (1977)				
SK	3	3	5	3
Heparin	2	2	2	3

As for the causes of death in the above mentioned patients venous thrombosis had been noted in one as a contributory cause. However he died several years after treatment in the coded series.

Summing up 13 patients treated with SK and 6 treated with heparin took part in the late review.

## METHODS

The re-examination included personal interview, physical examination, foot volumetry and phlebography.

**Interviews** The patients were questioned concerning the duration of their illness caused by DVT as well as any complications and operations.

**Physical examination** included careful inspection for varicose veins, hypostatic eczema, ulcerations and difference between the circumferences of the calves. The patients were classified according to the following criteria: 0) No change; 1) Moderate changes with oedema, varicose veins, hypostatic eczema and a difference of up to 1.5 cm between the greatest circumferences of the calves; 2) Severe or more pronounced changes than in the moderate cases, ulcerations and a more marked difference between the greatest circumferences of the calves.

The function of the venous system was assessed from changes in the volume of the foot—*foot volumetry*—with an apparatus designed by Thulesius et al. (22) and tried out clinically by Norgren (12). The parameters used are: EV = volume expelled (ml) as calculated from the reduction of foot volume during exercise;  $EV_{rel}$  = volume expelled relative to foot volume (ml/100 ml);  $\dot{Q}$  = rapid phase of refilling flow after exercise, flow relative to foot volume (ml/100 ml × min);  $\dot{Q}/EV_{rel}$  = time factor ( $\text{min}^{-1}$ ).

The control series consisted of 30 observations in 15 persons aged 14-42 years and a sample (14 observations) of 7 older individuals aged 58-72 years—Norgren (12) having shown that the reduction in volume is significantly smaller in elderly persons while restitution of the flow is the same in both groups. The mean values and S.D. of the volumetric findings in the control groups are given in Table II.

**Phlebography** was performed according to a

standardized technique (13). The phlebogram was examined for postthrombotic changes of the deep veins. Postthrombotic changes and incomplete flow in the iliofemoral veins are betrayed by retrograde flow in the contrast medium during the act of straining and irregularities of the veins and absence of valves.

Physical examinations and volumetric measurements were carried out in 1977. If phlebography follow-up had shown postthrombotic changes, phlebography of the valves and collateral vessels was not included in the review.

## RESULTS

### Series I (Table III)

This series consisted of 5 patients, 3 of whom had been treated with SK and 2 with heparin. The dosage of SK (50 000 IU/h for 12 h) was the same as in Series II. The phlebograms obtained after treatment showed no signs of thrombolysis. In none of the patients was the affected leg completely asymptomatic at the review in 1977. No difference in subjective symptoms between the SK- and heparin-treated patients

Table II Volumetric parameters in the control groups (mean ± S.D.)

	Control groups	
	Aged 16-42 (n=30)	Aged 58-72 (n=14)
EV (ml)	14.9 ± 4.6	11.7 ± 4.1
$EV_{rel}$ (ml/100 ml)	1.4 ± 0.4	1.1 ± 0.3
$\dot{Q}$ (ml/100 ml × min)	2.5 ± 1.0	2.6 ± 1.1
$\dot{Q}/EV_{rel}$ ( $\text{min}^{-1}$ )	2.0 ± 1.3	2.5 ± 1.0

### Series II (Table III)

Series 6 patients remained but one had developed severe arterial insufficiency in the legs and was omitted. Of the 5 patients available for investigation 3 had been treated with SK and 2 with heparin. A high dose of SK (100 000 IU/h as maintenance dose) had been given for a relatively long time (24 hours). In only one patient (no. 4) did phlebography show thrombolysis after treatment in proximal part of the calf veins and popliteal vein. No postthrombotic changes were seen at the phlebography in 1977. This was the only patient who had no symptoms at the time of the review. Patient 8 who had had thrombosis of both legs on two occasions and had been treated each time with heparin showed hardly any postthrombotic changes clinically or phlebographically at the re-examination. In patient 16—who also had had DVT in both legs on two occasions and who had not been treated for the first episode in one limb but had been treated with SK on the second occasion—the postthrombotic changes were the same in both limbs.

### Series III (Table III)

Series 8 patients remained (8 treatments) plus 3 from the supplementary series in which all patients were treated with SK. The period of treatment was 72 hours. Of the 11 patients with SK 6 showed thrombolysis in the calf and 2 (the same patient with DVT on two occasions in different legs) showed significantly more thrombolysis of the thrombus in the limb treated with SK than in the other treated with heparin. Cases 10 and 11 (also the same patient first treated with heparin and within 2 weeks with SK for progress of DVT in the same leg) showed after the SK treatment only a slight thrombolysis of no clinical importance. Patient 15 treated on one occasion with heparin because of DVT of one leg and later with SK because of a similar affection of the other leg showed no further change after the SK treatment. Patient 22 who also served as his own control had improved significantly better to SK. At the follow-up examinations thus showed an improvement of the veins after SK as well as heparin treatment. The patients with initial thrombolysis showed clinical changes of moderate and severe type less commonly than those who had not had any thrombolysis. Table IV summarizes the results of the treatments in the different series according to the clinical status at the reinvestigation.

The patients with thrombolysis had no or insignificant postthrombotic symptoms while those who had had no lysis showed postthrombotic changes.

## DISCUSSION

SK has been used as a thrombolytic agent for more than 15 years yet there is still much controversy about the value of such treatment. Many authors have reported complete lysis in a high percentage of these cases (6, 8, 9, 15). However treatment with SK is expensive and more often attended by side effects than treatment with heparin. Since several years may pass before the postthrombotic syndrome appears (21) proper evaluation of any advantage of SK must be based on reviews carried out long after termination of the initial treatment. But such reviews are few and some of them have been done rather early after treatment (Kakkar et al (9) 6–12 months; Olow et al (14) 1–10 months (no control group); Porter et al (15) 3–12 months; Bieger et al (3) 3–4 months; Johansson et al (8) 6–50 months (no control group)).

In the present study the coded series were reviewed 8–14 years after treatment. The number of patients examined was fairly small—only 19. In series I and II altogether 10 patients the dose of SK given was smaller than that conventionally recommended. Thus the patients in series I were given a maintenance dose of 50 000 IU/h for 12 hours and the patients in series II 100 000 IU/h for 24 hours. No thrombolysis was demonstrable on phlebographies taken immediately after the treatments nor were there less postthrombotic symptoms in the SK group at the late follow-up investigation. SK treatment that lasts for only 12 or 24 hours is obviously not long enough. In a phlebographic study Olow et al (14) found that complete thrombolysis required treatment for 72–96 hours. Such lengthy treatment (100 000 IU/h for 72 hours) was given to the patients in our series III and the supplementary series. It was obvious that thrombolysis could be achieved with this regimen. The initial standard dose in the supplementary group (500 000 IU) seems to be adequate since only one of the patients in the three coded series treated by Robertson (16) had a total dose of SK of more than 250 000 IU. These findings are in accordance with those of Olow et al (14) and Schmutzler (20). Of special interest in series III an

Table III *Reinvestigated patients: the effect of initial treatment and conditions at review in 1977*  
R: right L: left P: pathological N: normal

Follow up in 1977									
Case no	Treat ment	Affect ed limb	Phlebo gram after treatment	On sick leave	Clin cal symptoms	EV <sub>75</sub> (ml/ 100 ml)	Q (ml/ 100 ml ×min)	Q/EV <sub>75</sub> (min <sup>-1</sup> )	Phlebo gram
Series I									
11	1963 SK	R	St quo	Earlier ret red at 60 y (asthma)	R 1 L 1	P P	N P	P P	1964 st
12	1963 SK	R	St quo	4 mo	R 1 L 2	Not performed (gonarthrosis)			1965 st
14	1964 Heparin	R	St quo	2 weeks	R 1 L 1	Refused investigations			1977 st
17	1965 SK	L	St quo	2 y	L 1 R 1	P P	P P	P P	1969 st 1970 st
20	1965 Heparin	L	St quo	4-6 weeks	L 1 R 1	P N	P P	P P	1966 st
Series II									
2	1965 SK	L	St quo	2 weeks	L 1	N	P	P	St pos
4	1966 Heparin	L	Lysis	Ret red	L 0	Not performed (Coxarthrosis)			Normal
8	1966 Heparin	R	St quo	1 week	R 1 L 1	N N	P P	P P	Normal Deep v
14	1966 SK	R	St quo	7-8 mo	R 2	P	P	P	1967 st st pos
15	1966 SK	R	?	1 mo		Not performed			
16	1967 SK	L	St quo	2-3 mo	L 1 R 1	N P	P N	P P	Refused
Series III and supplementary series									
1	1967 Heparin	L	Lysis	4-6 weeks	0	P	N	P	Refused
2	1967 SK	R	Lysis	4-6 weeks	0	P	P	P	Refused
4	1967 Heparin	L	St quo	6 mo	2	P	N	P	St pos
7	1968 SK	R	Lysis	2-3 weeks	(1)	P	N	P	Refused
10	1968 Heparin	L	St quo						
11	1968 SK	L	Lysis 5 cm	4 weeks	(1)	P	P	P	Refused
14	1968 SK	L	Lysis 32.2 cm (progr 4 d after SK inf)	Retired	0	Not performed (senile tias)			1971 st but not
15	1968 SK	R	St quo (progr 4 d after SK inf)	1 y	R 1 L 1	N N	P P	P P	1971 st
17	1968 SK	R	Lysis 23.5 cm	2-3 weeks	(1)	N	P	P	1971 no signs
21	1969 SK	L	Lysis 20 cm	2-3 weeks	0	P	P	P	1971 st but not
22	1969 SK	R	Lysis 20 cm		R 0 L (1)	N P	N P	N P	1971 st but not

\* Criteria 0-2: see Methods

Table IV Comparison between the different types of treatments initial effects and clinical condition at the late investigation

Clinical status	Initial effect	Type of treatment			
		Heparin	SK 12 h	SK 24 h	SK 72 h
0	6 lysis 0 st quo	2			4
(1)	3 lysis 0 st quo				3
1 or 2	0 lysis 11 st quo	4	3	3	1

\* Criteria 0-2 defined in Methods

plementary series are 3 patients (nos 1 2 (the same patient) 15 and 22) who were treated with SK on one occasion for DVT in one leg and with heparin on another occasion for DVT in the other leg. Two of them (the first and the last case) showed a significantly better response to SK than to heparin; the third showed no difference.

When partial or complete thrombolysis is achieved in the femoral vein and proximal thereto, most phlebologists agree that no severe post-thrombotic symptoms, e.g. ulcerations, need be feared even if postthrombotic sequelae occur in the popliteal and calf veins (1-7). Our patients, in whom the femoral thrombus had been lysed but who displayed remnants in the distal veins, presented only fairly mild or no changes with slight oedema and/or small varicose veins. This is in agreement with the follow-up investigations by Widmer et al. (24) who found that none of their patients who demonstrated a partial thrombolysis developed crural ulcer.

Summing up, severe postthrombotic symptoms seemed to be less common in the group treated with SK for 72 hours and the complications of the thrombosis were more severe in patients treated with heparin or SK for only 12 or 24 hours (Table IV).

#### ACKNOWLEDGEMENTS

This investigation was supported by grants from the Swedish Medical Research Council (B79-19X-00087 15B) and the Donation Funds, Department of Pathology, University of Lund, Sweden.

## REFERENCES

- 1 Arnoldi C The venous return from the lower leg in health and in chronic venous insufficiency *Acta Orthop Scand (Suppl)* 64 1964
- 2 Bauer G A roentgenologic and clinical study of the sequelae of thrombosis *Acta Chir Scand (Suppl)* 61, 1940
- 3 Bieger R Bockhout Mussert R J Hohmann F & Loeliger E A Is streptokinase useful in the treatment of deep vein thrombosis? *Acta Med Scand* 199 81 1976
- 4 Browse N L Thomas M L & Pim H P Streptokinase and deep vein thrombosis *Br Med J* 3 717 1968
- 5 Common H H Seaman A J Rosch J Porter J M & Dotter C T Deep vein thrombosis treated with streptokinase or heparin *Angiology* 27 645 1976
- 6 Duckert F Muller G Nyman D Benz A Prisinger S Madar G da Silva M A Widmer L K & Schmitt H E Treatment of deep vein thrombosis with streptokinase *Br Med J* 1 479 1975
- 7 Haeger K Venous and lymphatic disorder of the leg *Scandinavian University Books* Stockholm 1966
- 8 Johansson E Ericson K & Zetterquist S Streptokinase treatment of deep venous thrombosis of the lower extremity *Acta Med Scand* 199 89 1976
- 9 Kakkar V V Flanc C Howe C T O Shea M & Flute P T Treatment of deep venous thrombosis. A trial of heparin streptokinase and Arvin *Br Med J* 1 806 1969
- 10 Kakkar V V Howe C T Laws J W & Flanc C Late results of treatment of deep vein thrombosis *Br Med J* 1 810 1969
- 11 Nilsson I M & Olow B Fibrinolysis induced by streptokinase in man *Acta Chir Scand* 123 247 1962
- 12 Norgren L Functional evaluation of chronic venous insufficiency by foot volumetry *Acta Chir Scand (Suppl)* 444 1974
- 13 Nylander G Venography of the lower extremities *In: Angiology* (ed H Adams) 2nd ed p 1251 Little Brown & Co Boston 1971
- 14 Olow B Johansson C Andersson J & E Deep venous thrombosis treated with a age of streptokinase *Acta Chir Scand* 136 11
- 15 Porter J M Seaman A J Common H H J Eidemiller L R & Calhoun A D C of heparin and streptokinase in the treatment of venous thrombosis *Am Surg* 41 511 1975
- 16 Robertson B R On thrombosis thrombo fibrinolysis I Thrombolytic therapy of deep thrombosis II Assay of individual fibrin sponse *Acta Chir Scand (Suppl)* 421 1971
- 17 Robertson B R Nilsson I M & Value of streptokinase and heparin in acute deep venous thrombosis *Acta Chir Scand* 134 203 1968
- 18 — Thrombolytic effect of streptokinase by phlebography of deep venous thrombosis *Acta Chir Scand* 136 173 1970
- 19 Robertson B R Nilsson I M Ny Olow B Effect of streptokinase in patients with deep venous thrombosis *Acta Chir Scand* 133 205 1967
- 20 Schmutzler R Thrombolytic treatment peripheral arterial and venous occlusions *Acta Chir Scand* 136 119 1968
- 21 Sigg K Varizen *Ulcus Cruris und Thrombosen* 158 Springer Verlag Berlin Heidelberg York 1968
- 22 Thulesius O Norgren L & Gjores J volumetry a new method for objective of edema and venous function *Vasa* 2 325 1973
- 23 Tsapogas M J Peabody R A W Karmody A M Devaraj K T & Eckert A controlled study of thrombolytic therapy in thrombosis *Surgery* 74 973 1973
- 24 Widmer L K Madar G Widmer M T H E & Duckert F *Tiefe Thrombosen. Aktuelle Probleme in der Angiologie* 33 Becken und Beinvenenthrombosen (ed L Huber & H Huber) p 121 Huber Bern S Wien 1975

# Blood Pressure in 60-Year-Old Men

*Findings in a Health Survey and Some Comparisons  
with 50 Year Old Men in the Same Community*

U Waern and H Åberg

*From the Department of Internal Medicine University Hospital Uppsala Sweden*

**ABSTRACT** A population survey of 60 year-old men ( $n=331$ ) was performed in Uppsala. The prevalence of hypertension defined as established hypertension and those having an unknown diastolic blood pressure (DBP) of  $\geq 105$  mmHg was 19.3%. Of the entire population 35.9% had not been detected previously. In the treated group 43.9% were controlled regarding the BP level. Thus 64.1% of the total hypertensive population at the age of 60 were either undetected or inadequately controlled.

Excretion of urinary electrolytes was also studied in this work. All participants of the health survey except four performed a 24-hour collection of following the health examination. Care was taken with endogenous creatinine clearance. Negative significant correlations were noted between excretion of sodium and potassium in urine and DBP. In the group ( $n=23$ ) of untreated hypertension. In a population sample ( $n=135$ ) of healthy men devoid of medical treatment in the same community survey, a positive and significant correlation was noted between the systolic BP and the urinary excretion of sodium. Thus up to a certain BP there is a pressure diuresis and at higher BP the kidney retains electrolytes.

**Keywords:** essential hypertension, urinary electrolytes, sodium intake, hypertension.  
*Acta Med Scand* 206: 99-105, 1979.

Increased blood pressure (BP) has been found in epidemiological studies to be a major risk factor for cardiovascular and cerebrovascular disease.

Thus it is an important task to find the hypertensive population and to commence treatment.

In an attempt to reduce the high cardiovascular morbidity and mortality in middle aged men, hypertension should naturally be treated before the advanced age is reached.

In the present study a 60-year-old male population

was screened. The purpose was to compare the 60-year-old hypertensive men with a 10 years younger group of men in the same community (13) as well as to perform some special studies on the excretion of urinary electrolytes. This survey was thus directed more towards research and eradication of symptoms arising from already established cardiovascular morbidity than towards purely preventive measures. For cerebrovascular morbidity the treatment of hypertension at this age has several preventive aspects (16). It is likely that in this age group there will be more cases of secondary hypertension than of the usual essential hypertension.

## STUDY POPULATION

Between Aug. and Dec. 1975 all men living in Uppsala and born in 1915 were offered a health examination. Out of a population of 422 men 331 arrived. Thus the participation rate was 78.4%. The screening procedures have been described elsewhere (26).

Hypertension was defined as a diastolic BP (DBP) of 105 mmHg or more. This limit was chosen to correspond with that of 50-year-old men in the same community (13). Pure systolic hypertension (SHT) was studied separately in a further group not included in the other hypertensive groups and was named SHT group comprising men with a systolic BP (SBP) of  $\geq 175$  mmHg and a DBP of  $< 105$  mmHg. None of the subjects in the SHT group were on antihypertensive treatment. Subjects who at the time of investigation were already on treatment for hypertension were also included in the hypertensive population.

**Abbreviations:** BP = blood pressure, DBP = diastolic BP, SBP = systolic BP, SHT = systolic hypertension, GFR = glomerular filtration rate, ECG = electrocardiogram, HR = heart rate,  $C_{cr}$  = creatinine clearance.

**Requests for reprints to:** A. U. Waern M.D., Department of Internal Medicine, University Hospital, S-750 14 Uppsala 14, Sweden.

Table I Blood pressures (mmHg) and heart rates (beats/min) in treated and untreated hypertensive SHT group and in the remaining population sample (mean  $\pm$  S D)

	Hypertensives		SHT (n=10)	Remaining population sample (n=257)
	Treated (n=41)	Untreated (n=23)		
SBP	166.7 $\pm$ 19.4***	177.0 $\pm$ 21.9***	183.0 $\pm$ 9.5***	137.4 $\pm$ 16.2
DBP	100.4 $\pm$ 9.3***	109.1 $\pm$ 4.4***	92.5 $\pm$ 5.4***	82.9 $\pm$ 8.3
HR	64.6 $\pm$ 8.3	67.7 $\pm$ 11.9	73.0 $\pm$ 20.6	66.7 $\pm$ 9.8

\*\*\* $p < 0.001$  compared to remaining population sample

## METHODS

### Blood pressure measurements

The BP and heart rate (HR) were recorded after 10 min of supine rest and the sitting BP was measured after another 2 min. A mercury manometer (Kifa Ercameter wall model) with a rubber bladder (cuff 12 cm wide and 35 cm long) was used. The BP was measured on the right arm and read to the nearest 5 mmHg. The DBP was recorded at the disappearance of the Korotkoff sounds (phase 5).

The examination took place at 7.00–8.30 a.m. and all BPs were recorded by the same registered nurse who took part in the previous screening of 50-year old men (13).

### Medical history

The medical history was obtained by means of a modified self-administered questionnaire ad modum Collen and by a direct personal interview. Information was gathered on hereditary aspects, previous diseases, drug intake, smoking habits and stress symptoms.

### Anthropometric measurements

Weight was measured without shoes and weight in underclothes. The heights and weights of the previously examined 50-year old men (13) were used as references for the relative body weight index. The subscapular skinfold thickness was measured in the sitting position with a Harpenden caliper (9).

### Statistical methods

Conventional statistical methods were used in estimation of mean and S D. Significance of difference between mean values was estimated according to Student's *t*-test (two tailed).

### Laboratory investigations

The following laboratory investigations were performed: Serum haematocrit, ESR, glucose, inorganic phosphate, cholesterol, albumin, creatinine, calcium, uric acid, gamma-glutamyl transferase. Urine: Urinary albumin excretion (UAE), Creatinine clearance (CrCl), Clinistix® volume per 24 h and 24-hour values of potassium, calcium, phosphate, magnesium, sodium, ethyl alcohol. Blood samples were taken in the morning. A 24-hour urine sample was collected from 32 subjects entering the screening. None of those who entered the screening or had a resting DBP of  $\geq 105$  mmHg. This was done to reduce possible errors caused by inadequately timed collections or variations in electrolyte excretion. Body size or differences in glomerular filtration rate (GFR) the values were related to the simultaneously obtained 24-hour creatinine clearance ( $CrCl$ ) formula given by Nordin et al. (20).

A 12-lead resting electrocardiogram (ECG) was recorded in all participants. Leads I, II, III, aVR, aVL, aVF, V<sub>1</sub>–V<sub>6</sub> were used. The ECGs were interpreted by a physician.

Table II Anthropometric measurements and laboratory findings

Body weight index is based on the findings in the 50-year old men in the same community (13)

	Hypertensives						Rem popu samps
	Treated		Untreated		SHT		
	Mean	S D	Mean	S D	Mean	S D	
Body weight index	1.07***	0.09	1.06*	0.10	0.94**	0.07	1.0
Subscapular skin fold thickness (mm)	18.9***	8.2	14.3	5.6	13.7	8.2	13.4
Triglycerides (mmol/l)	2.3*	1.8	2.0	1.1	1.8	1.2	1.6
Cholesterol (mmol/l)	6.4	1.3	6.6	1.3	6.9*	1.2	6.1
Blood glucose (mmol/l)	5.4	2.0	5.0	2.0	5.7	0.7	5.4
Urate ( $\mu$ mol/l)	309.4**	65.5	267.8	59.5	238.0	41.7	267.8

\* $p < 0.05$  \*\* $p < 0.01$  \*\*\* $p < 0.001$  compared to remaining population sample

### III Correlations between BP and urinary excretion of sodium potassium calcium and magnesium made for endogenous creatinine clearance) in 24 hour samples

	Untreated (n=23) (DBP)		Untreated + SHT (n=33) (DBP)		Population sample (n=135) (SBP)	
	r	p	r	p	r	p
1	-0.372	<0.05	-0.248	<0.05	0.168	<0.05
um	-0.528	<0.01	-0.281	<0.05	-0.088	>0.05
n	-0.313	>0.05	-0.264	<0.05	0.053	>0.05
um	-0.251	>0.05	-0.342	<0.01	-0.147	<0.05

physicians independently at the Department of  
Physiology and coded according to the Minnesota

## RESULTS

### Prevalence of hypertension

In the personal interview and in the self  
administered questionnaire 41 men (12.4%) re-  
ported an established hypertension. In addition at  
screening 23 men (6.9%) had a previously un-  
resting DBP of 105 mmHg or more. Thus the  
prevalence of hypertension was 19.3%. Ac-  
cording to the WHO criterion  $\geq 160/95$  mmHg 116  
(35.0%) were hypertensive.

### Heart rate and treatment for high BP

The mean SBP was 166.7 mmHg in the previously  
untreated group (n=41) and 177.0 mmHg in the un-  
treated group (n=23) (Table I). These values were  
significantly higher ( $p < 0.001$ ) than the mean value  
of 144 mmHg in the remaining population sam-  
ple (n=257 excluding the SHT group). The mean  
DBP was also significantly higher ( $p < 0.001$ ) in the

hypertensive groups than in the population sample.  
The distribution of the BPs among the total age  
group has been reported elsewhere (26). From this  
it may be noted that 10.3% had a SBP of  $\geq 175$   
mmHg and 6.9% had a DBP of  $\geq 110$  mmHg.

The mean HR was very similar in the treated  
untreated and SHT groups though the treated  
hypertensives had a somewhat but not significantly  
lower mean value. The SHT group had a mean  
resting HR of 73 beats/min. Twenty-five men were  
being treated with  $\beta$  blocking agents either as a  
single drug or in combinations. 11 were on saluretic  
treatment alone. Twenty-three men (56.1%) who  
had a DBP of  $< 105$  mmHg at screening were con-  
sidered to be adequately controlled.

### Other information from questionnaires and interviews

Slightly more than twice as many men in the treated  
group than in the remaining population sample  
reported that their fathers had died from myocardial  
infarction. The prevalence of reported hypertension  
was also significantly higher amongst fathers and

### IV Occurrence (%) of ECG abnormalities according to the Minnesota code (23) (Roman numerals) subjects had more than one abnormality)

	Hypertensives			Remaining population sample (n=257)
	Treated (n=41)	Untreated (n=23)	SHT (n=10)	
Normal ECG	26.8	17.4	40	12.8
1. Axis deviation (I)	2.4	—	10	1.6
2. Axis deviation (II)	9.8	8.6	—	1.9
3. QRS amplitude (III)	9.8	8.6	10	2.7
4. ST depression (IV)	7.3	8.6	10	1.9
5. ST depression (V)	19.5	8.6	30	6.2
6. Conduction defects (VI)	2.4	4.3	—	0.4
7. Atrial conduction defects (VII)	2.4	—	—	1.9
8. Qthym (VIII)	4.8	4.3	20	4.7
9. Miscellaneous (IX)	—	4.3	—	1.2



Table V Comparison of BP levels (mmHg) and HRs (beats/min) in 50 and 60 year old men in (mean  $\pm$  S D)

	50-year-old men		60-year-old men	
	Total population (n=2322)	Remaining population sample (n=1988)	Total population (n=331)	Remaining population sample (n=257)
SBP	133.2 $\pm$ 18.1	131.5 $\pm$ 16.5	145.2 $\pm$ 22.4	137.4 $\pm$ 16.2
DBP	83.7 $\pm$ 11.2	82.7 $\pm$ 10.2	87.2 $\pm$ 11.6	82.9 $\pm$ 8.3
HR	68.9 $\pm$ 10.7	68.4 $\pm$ 10.4	66.7 $\pm$ 10.3	66.7 $\pm$ 9.8

brothers of the men in the treated and untreated groups than in the remaining population sample.

Angina pectoris diagnosed by a physician was reported by 19.5% in the treated group and by 10.1% in the remaining population sample. Three men (30%) in the SHT group had angina pectoris.

In the group of untreated hypertensives, nine had consulted a physician for various reasons during the year of the screening and seven during the year before (1974). Nineteen had attended the general health examination the last time they were called. Twelve of the 19 were considered then to be hypertensives.

In the previously treated group, 11 men (26.8%) stated that they often felt stressed. The corresponding figures for the group with previously unknown hypertension and for the remaining population were 7 (30.4%) and 39 (15.2%) respectively.

Twelve men (29.3%) in the treated group and four (17.3%) in the untreated group were smokers. There were no differences between the adequately treated hypertensives ( $n=23$ ) and the treated group ( $n=18$ ) with a DBP of  $\geq 105$  mmHg with regard to the occurrence of other diseases, stress symptoms or smoking habits.

An increase in body weight by more than 10 kg since the age of 30 was noted by 17 men (73.9%) in the untreated group and by 19 (46.3%) in the treated. In the remaining population sample, 75 men (29.1%) reported such an increase.

#### Anthropometric measurements

The treated group had a relative body weight index of 1.07, which was significantly higher ( $p<0.001$ ) than in the non-hypertensive population sample (Table II). In the untreated group, this index was 1.06, which was also higher ( $p<0.05$ ) than in the non-hypertensive sample. The SHT group had an

index of 0.94, which was significantly ( $p<0.01$ ) than in the non-hypertensive sam-

#### Laboratory investigations

**Serum measurements.** Serum urate was pected significantly higher ( $p<0.01$ ) in the group than in the non-hypertensive population sample (Table II). The serum triglyceride cholesterol values were all higher in the treated hypertensives than in the non-hypertensives.

**Urine measurements.** The correlations between BP and urine electrolytes are given in Table III. A positive significant correlation was found between supine SBP and urinary sodium ( $r=0.168$ ) in a group of 135 healthy men (with no disease or medication). These 135 subjects were selected at random from participants in the screening of 60-year-old men fulfilling the criteria mentioned. In the group of untreated hypertensives, a negative significant correlation ( $r=-0.372$ ,  $p<0.01$ ) was found between sitting DBP and urinary sodium. A negative significant correlation ( $r=-0.528$ ,  $p<0.01$ ) was found between urinary sodium excretion and sitting DBP in the group of treated hypertensives. When the SHT and the untreated group were combined, the same pattern was again noted with negative correlations between sodium and potassium excretion and sitting DBP (Table III). A correlation was found between sitting DBP and urinary excretion of calcium ( $r=-0.264$ ,  $p<0.01$ ) and magnesium ( $r=-0.342$ ,  $p<0.01$ ) in the combined group.

Alcohol was detected in the urine of 11.0% in the total material and in 22.0% in the treated hypertensives. There was no significant difference in the mean BP level between the treated hypertensives with alcohol in the urine and the remaining treated hypertensives.

35 were considered pathological in 26.8% of treated hypertensives and in 40% of the SHT (Table IV)

## DISCUSSION

One of the purposes of this study was to compare the 60-year-old men with their 50-year-old counterparts. The typical BP development to a certain mean SBP in the older age group was found (mean SBP 145.2 and 133.2 mmHg respectively) and the DBP values were nearly identical (95.5 and 94.5 mmHg). This finding is in accordance with many reports (3, 5, 10, 14, 19, 22, 23, 29). Care must be taken, however, when comparing absolute BP values between various studies, and it is preferable to follow up one group of subjects over the years. In a recent comparison, however, some of the possible errors could be excluded. For instance, the measurements were performed by the same nurse, at the same facilities in the same outpatient

clinic. *et al.* (3) have shown that the average SBP in males between 15 and 25 years of age. It seems to remain stable until the age of 44, then it rises again until the age of 60 and then levels off. Nicol and Little (19) also found that there is no further increase in BP beyond that age. The finding of a lower mean HR ( $p < 0.01$ ) in the remaining population sample, and among untreated hypertensives in the 60-year-old group than among 50-year-old men is of interest. For the hypertensives it might be explained by a change in the hypertensive pattern, such as from a high cardiac output stage to a predominance of increased peripheral resistance. Another explanation might be a general decrease in the rate of the sinus node with

age. This was further considered of interest to make a comparative study of men with a systolic hypertension (SHT group). Although very small ( $n = 10$ ) this group deviated from the others in some respects: the mean serum cholesterol ( $p < 0.05$ ) and the glucose levels ( $p > 0.05$ ) in the SHT group were higher than those in the remaining population sample as well as in the other hypertensive groups. The mean body weight was lower. In addition, we noted a relatively high share of pathological changes. Most likely the high SBP in this subgroup is a symptom of an already manifested atherosclerotic disease. The above findings are in accordance

with the report by Kannel (14) that even isolated SHT is a powerful predictor of morbidity and mortality.

Previous studies (1, 13, 21) have convincingly shown that the majority of individuals with high BP are either undetected or inadequately treated. In this study 35.9% of the hypertensive population had not been detected before. In the previously treated group 43.9% were poorly controlled. Thus 64.1% of the total hypertensive population were either undetected or poorly controlled. This high rate is not encouraging, considering that many of these men had been investigated under other circumstances prior to the screening. This points to the necessity of further intensified education among the public as well as among all medical professionals dealing with BP measurements.

In this study the heredity showed a dominantly male line among treated hypertensives, whereas among the 10 year younger men the treated hypertensives mainly reported hypertension among mothers and sisters. Further, a higher proportion of men in the treated than in the untreated group among the 60-year-olds gave positive information on heredity. The reason for this is probably that hypertensives already under treatment have had more regular contact with a physician.

There appears to be a higher proportion of individuals with a weight gain of more than 10 kg since the age of 30 among hypertensives than in the general population. It would therefore seem to be a risk factor for hypertension. The possibility that the increase in weight is secondary to the hypertension *per se* cannot be totally ruled out.

Another purpose of the present report was to study the urinary content of alcohol and the excretion of some electrolytes. Alcohol has been shown to increase BP levels (7, 11, 25). Waern *et al.* (27) found that the mean SBP and DBP levels were somewhat higher ( $p > 0.05$ ) among 60-year-old men showing various indications of alcohol consumption. However, increased alcohol intake could also represent increased caloric intake and thus increased BP might be a function of increased body weight. However, in the treated group alcohol in the urine did not seem to affect the hypertension. In the group of untreated hypertensives who at the screening examination were informed of their high BP, none had alcohol in the urine on the following day. This could have been fortuitous, but it might also be related to the BP examination result.

When measuring various electrolytes in a 24 hour urine sample the reliability of the subject in making a complete collection is critical. For practical reasons it was not possible to collect urines in duplicate in this health examination. The urinary electrolyte excretion was therefore multiplied by a correction factor  $C_{cr}$  namely the endogenous creatinine clearance. Wibell and Bjorsell Östling (28) state that in good collectors endogenous creatinine clearance corresponds well with GFR at various ages. In large materials Healy (12) reported a linear regression between inulin clearance and  $C_{cr}$  thus making it possible to use  $C_{cr}$  in estimates of GFR. Having corrected the electrolyte excretion as mentioned above and knowing that the proportion of poor collectors was low the results should be reliable. The urinary electrolyte pattern has been studied previously in unselected health populations only with special regard to sodium (2). It is natural that this electrolyte has received most interest in view of its close relationship to the pathogenesis and maintenance of hypertension. There are reasons however for studying other electrolytes particularly as many antihypertensive drugs influence their excretion and might thus induce side effects. The effect of some saluretics on magnesium for example (8), needs further investigation. We studied therefore individuals of the same age and sex whose BP represented the whole spectrum from low to high aiming at detecting any abnormal handling of electrolytes by the hypertensive kidney.

We found a positive and significant correlation between the excretion of sodium and the SBP in the group of men with no known disease or medication. However in the group of untreated hypertensives there was a tendency towards a negative correlation. Similar findings concerning sodium excretion have been reported by Berglund et al (2). A possible explanation for this handling of sodium by the kidneys is that up to a certain BP level there is a pressure diuresis, and at higher BP levels the kidney retains electrolytes. Brown et al (4) and Schalekamp et al (24) have explained the deterioration of the renal ability to excrete sodium as secondary to an increased renovascular resistance. The results of our study seem to indicate that the kidneys are handling the other electrolytes in the same way.

The advantages of screening for hypertension at the age of 60 might be regarded as dubious. But according to figures published by Metropolitan Life

Insurance Company (15) therapeutic gains achieved even in these age groups. Thus expectancy for males at the age of 55 is reduced 6 years if the BP is 150/100 mmHg. Treatment of hypertension at this age might also be of value in reducing cardiovascular symptomatology as the incidence of cerebrovascular disease.

A further reason for screening for hypertension in 60 year olds is the assumption of an increased prevalence of secondary hypertension. Thus Lindholm et al (17) found such a trend in their study of 2422 hypertensives. Arteriosclerotic renovascular hypertension increased in their study from the age group 21–30 years to 33.4% in the 60 years group. Screening at the age of 60 will therefore reveal more cases of secondary hypertension. Screening at 50 years

## ACKNOWLEDGEMENTS

This work was supported by grants from C. J. W. Foundation at the Swedish Association of Physicians from the Faculty of Medicine at the University of Umeå.

## REFERENCES

- 1 Berglund G. Hypertoni och hypertens manifestationer hos 50-åriga män. En logisk och fysiologisk studie. Thesis. Kungälv 1974.
- 2 Berglund G, Aurell M & Wilhelmsson C. Renal function in normo- and hypertensive males. *Acta Med Scand* 199; 25: 1976.
- 3 Boe J, Humerfelt S & Wedervang F. Blood pressure in a population. *Acta Med Scand* 321: 1957.
- 4 Brown J J, Lever A F, Robertson J L, Schalekamp M A. Renal abnormality in hypertension. *Lancet* 2: 320: 1974.
- 5 Buhler R R, de Zeeuw D L, Schuler H, Weiler F, Baumann F & Schweizer W. Hypertensionproblem in der Schweiz. *Schweizer Med Wochenschr* 106: 99: 1976.
- 6 Collen M F, Cutler J L, Siegelbaum A L, R L. Reliability of a self administered questionnaire. *Arch Intern Med* 123: 664: 1963.
- 7 Dawber T R, Kannel W B, Kagan A, Dawber R K, McNamara P M & Paffenbarger H. Environmental factors in hypertension. In: *Epidemiology of hypertension* (ed J Stamler & T N Pullman) pp 275–279. Stratton New York 1967.
- 8 Editorial. Calcium, magnesium and diuretics. *J Intern Med* 169: 1975.
- 9 Edwards D A W, Hammond W H, Healy R, Tanner J M & Whitehouse R H D.

- uracy of calipers for measuring subcutaneous thickness *Br J Nutr* 9:133 1955
- over M E Fulgham J E & Simpson W G. Arterial hypertension in Northwest Florida: public health survey I. Methodology *Curr Ther Res* 11:1 1974
- stefberg F & Meyer J. Relationship between blood pressure and physical fitness. Smoking and alcohol consumption in Copenhagen males aged 40-60 *Acta Med Scand* 195:375 1974
- ily J K. Clinical assessment of glomerular filtration rate by different forms of creatinine clearance: a modified phenolsulphonphthalein excretion test *J Med* 44:348 1968
- strand H & Åberg H. Detection and characterization of middle aged men with hypertension *Acta Med Scand* 199:773 1976
- mel W B. Role of blood pressure in cardiovascular disease. The Framingham Study *Angiology* 26:15 1975
- v E A. High blood pressure: other risk factors and longevity. The insurance viewpoint *Am J Med* 28:11 1973
- rshall J. Hypertension and cerebrovascular disease. In: The management of cerebrovascular disease 200-209. Churchill, London 1968
- xwell M H, Blefer K H, Franklin S S & Brady P D. Cooperative study of renovascular hypertension. Demographic analysis of the study *MAA* 270:1195 1972
- ill W E & Chinn S. Screening for hypertension on epidemiological observations *Br Med J* 3:595 4 1974
- ol R O & Little P J. A study of the normal range of blood pressure in the aged New Zealanders *NZ Med J* 81:512 1975
- rdn B E C, Hodgkinson A & Peacock M. Measurement and meaning of urinary calcium *Orthop* 57:293 1967
- 71 Report of Inter Society Commission for Heart Disease Resources. Guidelines for the detection, diagnosis and management of hypertensive population *Circulation* 44:A763 1971
- 72 Rorive G, Kulbertus H & Demanet J C. Résultats préliminaires des enquêtes épidémiologiques concernant la fréquence de l'hypertension artérielle dans la population Belge *Rev Med Liege* 875 1975
- 23 Rose G A & Blackburn H. Cardiovascular survey methods. WHO Monogr Ser 56 1968
- 24 Schalekamp M A D H, Schalekamp M, Kuyken M P A, DeMoor Fruyter M, Meijner Th, Vaandrager Kranenburg D J & Berkenhager W H. Renin suppression in hypertension in relation to body fluid volumes, patterns of sodium excretion and renal hemodynamics *Clin Sci Mol Med (Suppl)* 1:783 1973
- 25 Shah V V. Environmental factors and hypertension with particular reference to prevalence of hypertension in alcohol addicts and teetotalers. In: The epidemiology of hypertension (ed J Stamler, R Stamler & T N Pullman) pp 204-217. Grune & Stratton, New York 1967
- 76 Waern U. Health and disease at the age of sixty. Findings in a health survey of 60-year-old men in Uppsala and a comparison with men 10 years younger *Ups J Med Sci* 83:153 1978
- 77 Waern U, Boberg J & Hellings K. Evaluation of indices of alcohol intake in a population of 60-year-old men in Uppsala *Acta Med Scand* 205:353 1979
- 78 Wbell L & Bjorsell-Östling E. Endogenous creatinine clearance in apparently healthy individuals as determined by 24-hour ambulatory urine collection *Ups J Med Sci* 78:43 1973
- 29 Wilber J A, Milward D, Baldwin A, Capron B, Silverman A, James L M, Wolbert T & McCombs N J. Atlanta community high blood pressure program: methods of community hypertension screening *Circ Res (Suppl)* 2:30 1972



# The Effects of a Beta<sub>1</sub>-Blocking Agent, Atenolol, on Blood Pressure, Plasma Renin Activity and Prostaglandin F<sub>2α</sub> Excretion in Patients with Essential Hypertension

T Pitkajarvi P Ylitalo T Metsa Ketela and H Vapaatalo

*From the Community Health Centre of Tampere and the Department of Biomedical Sciences University of Tampere Tampere Finland*

**ABSTRACT** The antihypertensive action of  $\beta$  blockers has been suggested to be associated with increase in plasma renin activity (PRA) and can be antagonized by indomethacin, a prostaglandin synthesis inhibitor. We studied the acute and chronic effects of a  $\beta_1$  blocking agent, atenolol (10-40 mg b.i.d.), on blood pressure (BP), PRA and  $\text{PGF}_{2\alpha}$  excretion in 12 male patients (40-60 years old) with essential hypertension. BP was measured by means of a brachial cuff. PRA and  $\text{PGF}_{2\alpha}$  were determined radioimmunologically. One day after initiation of atenolol treatment BP fell significantly from the supine values from 159/114 to 143/104 mmHg and the erect from 158/118 to 140/106 mmHg. After 6 weeks BP decreased further to 135/94 mmHg, respectively. After the cessation of treatment for three weeks BP rose to the pre-atenolol level. When the dose was readjusted (25-150 mg daily), diastolic BP remained at 100 mmHg or lower in only two patients. During the atenolol treatment PRA declined to one third of the pre-treatment level in one day and to one half in six weeks. Urinary excretion of  $\text{PGF}_{2\alpha}$  was not affected by treatment. Our results suggest that 1) the antihypertensive action of atenolol and the reduction of PRA are substantial already in one day, and 2) the decrease in BP or PRA is not associated with  $\text{PGF}_{2\alpha}$  excretion.

**KEY WORDS:** atenolol, beta-adrenergic blocking agents, plasma renin activity, prostaglandin excretion, hypertension.

branes stabilizing action (4-5). Its antihypertensive effect is also well documented (3, 7, 16, 17, 23, 24). The mechanism of the antihypertensive action of  $\beta$  blocking drugs is still unclear in detail, but decrease in cardiac output, effects on the central nervous system and inhibition of the renin-angiotensin system have been suggested (6, 35). Recently the antihypertensive action of  $\beta$  blocking drugs has been reported to be substantially antagonized by a prostaglandin (PG) synthetase inhibitor, indomethacin (8, 9). Thus PGs may also be involved in the antihypertensive action of  $\beta$  blocking agents.

In order to investigate the antihypertensive action of  $\beta_1$  blocking drugs in detail we studied the acute and long-term effects of atenolol on blood pressure (BP), heart rate (HR), plasma renin activity (PRA) and electrolyte excretion in patients with essential hypertension. It has been found previously that indomethacin decreases  $\text{PGF}_{2\alpha}$  excretion in hypertensive patients in close relation with PRA (36) and most probably also reduces PGE excretion (12). Since the determination of  $\text{PGF}_{2\alpha}$  with our methodological facilities is more reliable than that of PGE and evidence has been presented that  $\text{PGF}_{2\alpha}$  exhibits an excretion pattern similar to PGE (15, 33), we have measured the excretion of  $\text{PGF}_{2\alpha}$  also in the present study in order to obtain infor-

Acta Med Scand 206 107 1979

Adrenergic blocking agents are widely used in the treatment of essential hypertension (6, 28, 29). Atenolol is a  $\beta_1$  selective blocking agent which is devoid of intrinsic sympathomimetic and mem-

**Abbreviations:** PG = prostaglandin, PRA = plasma renin activity, BP = blood pressure, HR = heart rate,  $\text{Na}^+$  = sodium,  $\text{K}^+$  = potassium.

**Reprint requests to:** T Pitkajarvi, M.D., Community Health Centre of Tampere, Hämeenkatu 5 A, SF-33100 Tampere 10, Finland.



Fig 1 Design of the trial

mation on the action of atenolol on renal PG biosynthesis. The side-effects of atenolol were also taken into consideration.

## STUDY POPULATION AND METHODS

### Patients

Twelve male patients were studied. All had diastolic arterial pressures of at least 110 mmHg in health screening examinations arranged in Tampere, Finland, for men aged 40 years. In seven (58%) of the 12 patients, high BP values had been measured 1–12 years previously. However, none of the 12 patients had been treated with antihypertensive agents during the last six months. All the patients were aware of their participation in the study. They were asked to continue their ordinary life over the whole study period without any dietary restriction, except for abstaining from alcoholic beverages and fasting on the mornings of visits to the Outpatient Hypertension Clinic.

### Measurement of BP

The diagnosis of arterial hypertension was confirmed at the two initial visits to the Outpatient Hypertension Clinic of the Community Health Centre of Tampere. During the trial, BP was measured at an interval of three weeks between 8.50 and 9.20 a.m., first at rest after lying down for 5 min and then erect after standing for 2 min, two measurements being made in each position. Diastolic BP was measured at the fourth Korotkoff sound. HR was counted at the same time. BP was measured by one and the same physician at the same time on the same weekday in the right arm with the same brachial cuff and mercury manometer with an accuracy of 2 mmHg. The lowest of the two measurements was used for analyses. When the patients were treated with placebo or atenolol, they took their drugs 2.5 h before the BP measurement.

### Examinations

The following examinations were performed for the discovery of possible complications of the disease and for the exclusion of secondary hypertension: careful physical examination, inspection of the ocular fundi, ECG and chest X-ray with estimation of heart size. Eleven patients (92%) had 1st or 2nd degree hypertensive changes in the ocular fundi. Left ventricular hypertrophy was found in three patients by ECG and in one patient by chest X-ray. These four men (33%) were classified as WHO stage II. The laboratory examinations were as follows: ESR, haematocrit, Hb, erythrocytes, mean corpuscular Hb, mean corpuscular Hb concentration, mean corpuscular volume, reticulocytes, leucocytes, differential leucocyte count, platelets, prothrombin time (estimated by Sysplastin A), serum creatinine, serum aspartate and alanine

aminotransferases, serum alkaline phosphatase, glucose, serum antinuclear antibodies, serum  $\text{Na}^+$ , urinary protein, glucose, sediment and bacteria. They were determined just before and six weeks beginning of atenolol treatment. The did not reveal any signs of secondary hypertension.

### Design of the trial (Fig 1)

After a period of three weeks without any treatment, patients received placebo (single blind) for one tablet b.i.d. Thereafter, a fixed dose of atenolol was given b.i.d. (at 6.20 or 6.40 a.m.) for six weeks followed by 3 weeks without treatment. Finally, the patients received atenolol further 26 weeks, the doses being adjusted (25–150 mg daily). Atenolol tablets were supplied by Lääketehtävä Oy, Tampere.

PRA, urinary excretion of  $\text{PGF}_{2\alpha}$  and secondary  $\text{Na}^+$  and  $\text{K}^+$  were measured five times during the course of the trial: before and after the placebo period, one day and six weeks after the beginning of treatment, and three weeks after withdrawal of treatment. Serum  $\text{Na}^+$  and  $\text{K}^+$  were re-examined twice during additional atenolol treatment for 26 weeks.

### Determinations of PRA, $\text{PGF}_{2\alpha}$ and electrolytes

For the estimation of PRA, venous blood was drawn from the patients sitting at rest for 10 min before the BP measurement into cooled test tubes containing 0.1 N  $\text{Na}_2\text{EDTA}$ .  $\text{PGF}_{2\alpha}$ ,  $\text{Na}^+$  and  $\text{K}^+$  were determined in urine collected over the night for 12 h corresponding to the dose of placebo or atenolol. Plasma and urine samples were stored at  $-20^\circ\text{C}$  until analyzed.

PRA was determined in the Minerva Institute of Research, Helsinki, by radioimmunoassay of angiotensin I released in incubation as described by Unger et al. (13).  $\text{PGF}_{2\alpha}$  was extracted by Unger et al. (27) and measured by radioimmunoassay. Antigen-antibody complex was separated by precipitation with 10% trichloroacetic acid (TCA) of Gersham et al. (14). Recoveries were 100% using labelled  $\text{PGE}_1$  (sp. act. 53 Ci/mmol, Amersham). The cross-reactivity of antiserum was less than 0.02% with  $\text{PGE}_1$ . PC, serum and urinary  $\text{Na}^+$  and  $\text{K}^+$  were determined by photometry.

### Side effects

During the periods with or without active treatment, the subjective symptoms or side-effects were actively questioned and graded from I to III (mild to severe). New symptoms during treatment were recorded separately.

### Statistical methods

The mean values  $\pm$  S.E. were calculated. The differences between the means were evaluated by paired *t*-test. Regression equations were calculated by the method of least squares.

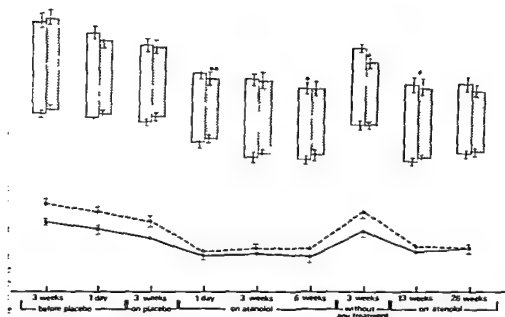


Figure 2. BP and HRs (mean  $\pm$  S.E.) prior to and during treatment of 12 male patients with essential hypertension. The columns represent systolic (top) and diastolic (bottom) BP in supine (□) and erect (◻) position

— Supine HRs    = erect HRs    \*  $p < 0.05$     \*  $p < 0.01$   
 \*\*  $p < 0.001$  as compared to the preceding BP or HR values

## RESULTS

### Pressure and heart rate

There was no significant decrease in BP between visits before the placebo period (Fig. 2). Mean systolic and diastolic BP in supine position increased slightly during the placebo period from 141/117 to 159/114 mmHg ( $p < 0.05$ ). One day after the beginning of atenolol treatment four of the patients became normotensive. Systolic BP fell below 100 mmHg in both positions. Compared to the BP during the placebo period the mean values of supine and erect BP decreased to 143/104 and 140/106 mmHg respectively ( $p < 0.01$ ). The corresponding decreases in heart rate were from 72 to 60 and from 78 to 61 beats/min. Three weeks later BP decreased further: supine to 135/94 mmHg and erect to 134/96 mmHg and five additional patients became normotensive. Also the supine HR tended to decrease further. When atenolol was withdrawn in all the patients the BP and heart rate rose in three weeks to the pre-atenolol level. No symptoms of withdrawal effect were observed. During an additional period of 26 weeks on

atenolol BP and HR decreased to the level before the drug discontinuation. In three patients the doses of atenolol could be reduced to 50 mg and in one to 25 mg daily without any notable reduction in the antihypertensive responses. In two patients the dose was raised to 150 mg daily but one of them and another patient receiving 100 mg atenolol daily still remained hypertensive (diastolic BP 100 mmHg or more in both positions) at the close of the trial. Thus a good antihypertensive effect was obtained in 83% of the cases.

### Plasma renin activity and prostaglandin $F_{2\alpha}$ excretion

There was no significant difference between PRA values before and after the placebo period (Table I). During the atenolol treatment PRA decreased in one day to almost one third of that on placebo. Six weeks later PRA values were still lower than during the placebo treatment but higher than those measured one day after the beginning of the atenolol therapy ( $p < 0.05$ ). When atenolol was discontinued PRA increased almost to the pre-atenolol level. No correlations between the falls in BP and PRA were



Table I Action of atenolol (50 mg b.i.d.) on PRA,  $\text{PGF}_{2\alpha}$  excretion, ratio PRA/ $\text{PGF}_{2\alpha}$  excretion,  $\text{Na}^+$  excretion, urine volume and serum  $\text{Na}^+$  and  $\text{K}^+$  in 12 male patients with essential hypertension (mean  $\pm$  S.E.)

	Before placebo	3 weeks on placebo	1 day on atenolol	6 weeks on atenolol	3 weeks withdrawal of atenolol
PRA (ng AI/ml $\times$ h <sup>-1</sup> )	113 $\pm$ 0.35	101 $\pm$ 0.78	0.38 $\pm$ 0.05*	0.54 $\pm$ 0.11*	0.81 $\pm$ 0.13
$\text{PGF}_{2\alpha}$ excretion ( $\mu\text{g}/12$ h)	1.65 $\pm$ 0.43	1.17 $\pm$ 0.17	1.35 $\pm$ 0.24	1.28 $\pm$ 0.27	1.31 $\pm$ 0.18
PRA/ $\text{PGF}_{2\alpha}$ ratio	0.74 $\pm$ 0.11	0.91 $\pm$ 0.19	0.44 $\pm$ 0.11*	0.77 $\pm$ 0.30	0.86 $\pm$ 0.14
$\text{Na}^+$ excretion (mmol/12 h)	126.9 $\pm$ 14.0	137.6 $\pm$ 8.9	126.6 $\pm$ 14.4	116.7 $\pm$ 15.4	139.1 $\pm$ 11.2
$\text{K}^+$ excretion (mmol/12 h)	34.3 $\pm$ 3.4	32.3 $\pm$ 2.8	37.3 $\pm$ 3.6	27.2 $\pm$ 3*	36.3 $\pm$ 3.1
Urine volume (ml/12 h)	691 $\pm$ 67	711 $\pm$ 56	707 $\pm$ 51	573 $\pm$ 54	644 $\pm$ 57
Serum $\text{Na}^+$ (mmol/l)	140.8 $\pm$ 0.7	141.5 $\pm$ 0.5	140.0 $\pm$ 0.5*	139.6 $\pm$ 0.6**	139.8 $\pm$ 1.1
Serum $\text{K}^+$ (mmol/l)	4.2 $\pm$ 0.1	4.3 $\pm$ 0.1	4.4 $\pm$ 0.1	4.3 $\pm$ 0.1	4.3 $\pm$ 0.1

\* $p < 0.05$  \*\* $p < 0.001$  as compared to values on placebo

found in single patients either one day or six weeks after the beginning of the atenolol treatment except between the falls in the erect diastolic BP and PRA after the six week atenolol treatment ( $r = 0.665$ ,  $p < 0.05$ ). Three weeks after the withdrawal of atenolol the individual increases in systolic or diastolic BPs in supine or erect positions did not correlate either with the rises in PRA. However when the correlation coefficients between the total of all measured PRA values ( $n = 58$ ) and corresponding BPs were determined the erect systolic BP values and the diastolic pressures in both positions correlated significantly to PRA ( $r = 0.284$ – $0.474$ ,  $p < 0.05$ – $0.001$ ).

There were no significant changes in  $\text{PGF}_{2\alpha}$  excretion during the course of the trial. The 12 hour urine of one patient was contaminated with semen and the corresponding  $\text{PGF}_{2\alpha}$  excretion value was exceptionally high. Consequently all the  $\text{PGF}_{2\alpha}$  excretion values of this patient were excluded. The ratio PRA/ $\text{PGF}_{2\alpha}$  excretion decreased substantially in one day during the atenolol therapy but no more six weeks later.

### Electrolytes

During the atenolol therapy serum  $\text{Na}^+$  decreased slightly but significantly in six weeks (Table I). After discontinuation of the drug it did not, however, return to the pre atenolol level. During additional treatment with atenolol for 26 weeks there were no significant changes in serum  $\text{Na}^+$  ( $140 \pm 0.5$  and  $141 \pm 0.5$  mmol/l, two measurements performed) as compared to the concentration on placebo. Serum  $\text{K}^+$  remained unchanged through the periods with and without atenolol also during the additional

drug period of 26 weeks ( $4.4 \pm 0.1$  and mmol/l). The urinary  $\text{K}^+$  excretion declined over weeks on atenolol treatment and increased when atenolol was discontinued. Both the excretion and the urine volume tended to increase during the six week period on atenolol. Total body weight decreased by 2 kg during the treatment and remained at the reduced level even during the three week period without atenolol.

### Other laboratory parameters

The various other laboratory parameters did not show any significant changes during treatment except for a slight increase in prothrombin time ( $p < 0.05$ ) from  $0.75 \pm 0.07$  to  $0.84 \pm 0.04$  s (measured by S-mplastin A).

### Side effects

The total number of patients with symptoms and the number of complaints were highest 9 and 19 respectively in the periods before placebo against 7 and 10 during the treatment period. They were of the same order of magnitude in the atenolol periods up to six weeks after treatment and increased again after withdrawal of the drug. During the atenolol treatment was reinstituted for two periods of 13 weeks only one or two patients exhibited together one or two symptoms.

Only one patient had a new symptom (dizziness) on the first day on atenolol. Two patients had new symptoms (weakness of legs, dry mouth, dizziness and slight diarrhoea) and two patients had new symptoms (dry mouth and cold extremities) during the following two treatment periods of 13 weeks respectively. After discontinuation

for three weeks the number of new symptoms increased again five new symptoms in five patients. No new side effects appeared when treatment was reinstituted for a further 26 weeks as compared to the complaints during the treatment without atenolol.

## DISCUSSION

The patient population of the present study was a homogeneous one consisting of middle aged otherwise healthy with established essential hypertension. None of them had received any antihypertensive treatment during the last six months, in most cases never at all or not for many

years. There was a marked fall in the systolic and diastolic blood pressures already one day after the initiation of atenolol treatment. A decrease in BP in one day has been reported also when e.g. pindolol or metoprolol was used (34). Atenolol and propranolol have been found to reduce BP substantially during three days of treatment (20, 21). Significant decreases in systolic and diastolic blood pressures were recently found in healthy volunteers already after 4 h respectively after administration of atenolol orally (100–200 mg), the decrease in systolic BP still being apparent 8 h and in diastolic BP 12 h after administration (11). The  $\beta$  blocking drugs e.g. atenolol reduce HR and consequently cardiac output (22) which would partly explain the fall in BP.

There was also a substantial decrease in PRA during atenolol treatment. In this study PRA was measured in sitting patients without any restriction on their food intake or normal daily life conditions better corresponded to their life conditions than e.g. recumbency or restriction before sampling. In spite of that the results are in agreement with the previous observations of falls in PRA caused by atenolol (1, 2, 26). In general there was only a poor correlation between the decreases in BP values and plasma renin levels in the individual patients during treatment and withdrawal of the drug did not result in any correlation between the increases in BP and PRA. No correlation between these parameters has been found in some other studies (2, 10, 20). The changes in PRA by atenolol have not been found to correlate either with plasma renin concentrations or changes in BP values in

supine or erect positions or during exercise (23). In addition in this study PRA increased slightly during the course of the atenolol treatment but BP decreased further. The above observations counteract the idea that the reduction in BP is dependent on PRA alone. On the other hand when the BP values fell during atenolol treatment the PRA values also fell and significant correlations were found between all the PRA values and the corresponding erect systolic BPs or the diastolic pressures in both positions. This suggests that the changes in BP caused by  $\beta_1$  blocking drugs at least partly occur concomitantly with the alteration in PRA (19).

Indomethacin treatment markedly suppresses  $\text{PGF}_{2\alpha}$  excretion by inhibiting biosynthesis of PGs. This is closely accompanied by the decrease in PRA (36). In the present study  $\text{PGF}_{2\alpha}$  was unaffected by atenolol but PRA was substantially decreased. This suggests that the decrease in PRA does not necessarily result in a reduction in  $\text{PGF}_{2\alpha}$  production although the opposite dependence between these parameters may exist. Evidence has been presented that  $\text{PGF}_{2\alpha}$  has an excretory pattern similar to  $\text{PGE}_2$ , another common renal PG (15, 33). Urinary  $\text{PGF}_{2\alpha}$  may thus at least to some extent reflect the overall excretion of PGs. It cannot however be excluded that the production of other members of PG series e.g.  $\text{PGI}_2$  and  $\text{PGG}_2$  which stimulate the renin release (31, 32) may be changed by  $\beta$  blocking drugs.

There was a significant decrease in  $\text{K}^+$  excretion during the atenolol therapy. Thus atenolol seems to spare  $\text{K}^+$  as other  $\beta$  blocking agents e.g. metoprolol may also do (30) although we did not find any significant increase in serum  $\text{K}^+$ . It is likely that this reduction in  $\text{K}^+$  excretion was due to the tendency of urine volume to decrease during atenolol treatment. A similar tendency was found in  $\text{Na}^+$  excretion but unexpectedly the serum  $\text{Na}^+$  concentration also decreased statistically significantly in six weeks. This decrease is however without marked biological significance especially since the discontinuation of atenolol treatment for three weeks did not cause an increase in serum  $\text{Na}^+$  and during an additional atenolol period of 26 weeks serum  $\text{Na}^+$  no longer differed from the values before atenolol. In spite of a tendency towards reduced diuresis the body weight of the patients decreased. Thus there was obviously no marked fluid retention. The discontinuation of atenolol for three weeks caused no renewed rise in body weight sug-

gesting that the patients were aware of their disease and readjusted their dietary habits

The side effects of atenolol were few and slight. All of the patients completed the trial and they still (about one year after the close of the trial) continue with the atenolol treatment.

The results indicate that atenolol decreases systolic and diastolic BP, HR and PRA in only one day and its antihypertensive effect becomes more marked during the following weeks. Atenolol has no effect on  $\text{PGF}_{2\alpha}$  excretion. The falls in BP and PRA are not associated with the excretion of  $\text{PGF}_{2\alpha}$ , but we cannot exclude the possibility that atenolol may have some action on the excretion of some other members of the PG series.

### ACKNOWLEDGEMENTS

This study was supported by a grant from the Orion and Medica Scientific Foundation, Helsinki, Finland, for the measurement of prostaglandins.

### REFERENCES

- 1 Åberg H. Plasma renin activity after the use of a new beta adrenergic blocking agent (ICI 66 082). *Int J Clin Pharmacol* 9: 98, 1974.
- 2 Amery A, Billiet L, Boel A, Fagard R, Reybrouck T & Willems J. Mechanism of hypotensive effect during beta adrenergic blockade in hypertensive patients. Hemodynamic and renin response to a new cardioselective agent, Tenormin or ICI 66 082. *Am Heart J* 91: 634, 1976.
- 3 Amery A, Billiet L, Jossens J, V Meekers J, Reybrouck T & Van Mieghem W. Preliminary report on the haemodynamic response of hypertensive patients treated with a beta blocker (ICI 66 082). *Acta Clin Belg* 28: 358, 1973.
- 4 Barrett A M. The pharmacology of atenolol. *Postgrad Med J (Suppl)* 3: 58, 1977.
- 5 Barrett A M, Carter J, Fitzgerald J D, Hull R & LeCount D. A new type of cardioselective adrenoceptive blocking drug. *Br J Pharmacol* 43: 340P, 1973.
- 6 Barnitt D W & Marshall A J. Treating hypertension. The place of beta blockade. *Br Heart J* 39: 821, 1977.
- 7 Douglas Jones A P & Cruickshank J M. Once daily dosing with atenolol in patients with mild or moderate hypertension. *Br Med J* 1: 990, 1976.
- 8 Durao V, Prata M M & Concalves L M P. Modification of antihypertensive effect of  $\beta$  adrenoceptor blocking agents by inhibition of endogenous prostaglandin synthesis. *Lancet* 2: 1005, 1977.
- 9 Durao V & Roco J M G T. Modification by indomethacin of the blood pressure lowering effect of pindolol and propranolol in conscious rats. *Pharmacol* 43: 377, 1977.
- 10 Epstein S E & Lubbe W F E. Atenolol on blood pressure and plasma renin activity in patients with moderate hypertension. *Med J* 52: 875, 1977.
- 11 Fitzgerald J D, Ruffin R, Smeds, Roberts R & McAinsh J. Studies on pharmacokinetics and pharmacodynamics in man. *Eur J Clin Pharmacol* 13: 81, 1977.
- 12 Frölich J C, Hollifield J W, Dom Frölich B L, Seyberth H, Michelis Oates J A. Suppression of plasma renin by indomethacin in man. *Circ Res* 39: 447, 1976.
- 13 Fyhrquist F, Soven P, Puutula L, U H. Radioimmunoassay of plasma renin. *Clin Chem* 22: 250, 1976.
- 14 Gersham H, Powers E, Levine L, Lisk H. Radioimmunoassay of angiotensin, digoxin, morphine and cyclic monophosphate with microcellulose. *Prostaglandins* 1: 407, 1972.
- 15 Gill J R, Frölich J C, Bowden R E, A Keiser H R, Seyberth H W, Bartter F C. Bartter's syndrome characterized by high urinary prostaglandin synthesis. *Am Med J* 61: 43, 1976.
- 16 Hansson L, Åberg H, Karlberg Westerlund A. Controlled study of treatment of hypertension. *Br Med J* 2: 3, 1977.
- 17 Hansson L, Karlberg B E, Åberg H, A Jameson S & Henningsen N C. Hypotensive effect of atenolol (ICI 66  $\beta$ -adrenergic blocking agent). *Acta* 199: 257, 1976.
- 18 Jaffe B M, Smith J W, Newton W C W. Radioimmunoassay for angiotensin. *Endocrinology* 171: 494, 1971.
- 19 Johnson B F, Smith K J, LaBrooy. The nature of the  $\beta$  adrenoceptor controlling plasma renin activity in man. *Clin Sci Mol Biol* 1976.
- 20 Lehtonen A. Atenolol in hypertension. *Scand J Clin Lab Invest* 2: 125, 1976.
- 21 Lehtonen A, Kanto J & Kleimola T. Concentrations of propranolol in patients with hypertension. *Eur J Clin Pharmacol* 11: 1, 1976.
- 22 Lund Johansen P. Haemodynamic long term effect of a new  $\beta$  adrenoceptor blocking drug (ICI 66 082) in essential hypertension. *Br J Clin Pharmacol* 3: 445, 1976.
- 23 Myers M G, Lewis G R J, Steiner J C T. Atenolol in essential hypertension. *Pharmacol Ther* 19: 502, 1976.
- 24 Petne J C, Galloway D B, Webster W T & Lewis J A. Atenolol and bendroflumethiazide in the treatment of hypertension. *Br Med J* 4: 133, 1975.
- 25 Sassard J, Pozet N, McAinsh J, Leg Zech P Y. Pharmacokinetics of atenolol with renal impairment. *Eur J Clin Pharmacol* 1977.

- ard J Pozet N Vincent M & Zech P Y  
 nolol and renin release *N Engl J Med* 294 787
- er G W Stamford I F & Bennett A Extrac  
 of prostaglandins from human blood *Nature*  
 id) 233 336 1971
- il Manning H J Experience with  $\beta$  adreno-  
 or blockers in hypertension *Drugs (Suppl)* 1  
 1976
- Hypertension Which beta blocker? *Drugs* 12 412
- Metabolic effects of  $\beta$  adrenoceptor blockers  
 gs (Suppl) 1 121 1976
- er P C Larsson C Anggård E Hamberg  
 Corey E J Nicolaou K C & Samuelsson B  
 ulation of renin release from rabbit renal cortex  
 rachidonic acid and prostaglandin endoperoxides  
 : Res 39 868 1976
- erton A R Misono K Hollisfield J Frolich J  
 C Inagami T & Oates J A Prostaglandins and  
 renin release I Stimulation of renin release from  
 rabbit renal cortical slices by  $\text{PGI}_2$  Prostaglandins  
 14 1005 1977
- 33 Williams W M Frolich J C Nies A S & Oates  
 J A Urinary prostaglandins Site of entry into renal  
 tubular fluid *Kidney Int* 11 256 1977
- 34 Wilson M Morgan G & Morgan T The effect on  
 blood pressure of  $\beta$ -adrenoceptor blocking drugs  
 administered once daily and their duration of action  
 when therapy is ceased *Br J Clin Pharmacol* 3 857  
 1976
- 35 Wollam G L Gifford J R & Tarazi R C  
 Antihypertensive drugs clinical pharmacology and  
 therapeutic use *Drugs* 14 420 1977
- 36 Ylitalo P Pitkajarvi T Metsä Ketela T & Va  
 paatalo H The effect of inhibition of prostaglandin  
 synthesis on plasma renin activity and blood pressure  
 in essential hypertension *Prostagl Med* 1 479 1978



# The Diagnostic Challenge of Left Atrial Myxoma

## Importance of Echocardiographic Screening

Jens Berning Henrik Egeblad Poul Laursen  
and Alf Wennevold

From Medical Department B and Surgical Department R, Rigshospitalet (University Hospital),  
Copenhagen, Denmark

**ACT** Left atrial myxomas are extremely difficult to diagnose since their variable manifestations consist of clinical entities more commonly seen in aortic stenosis, endocarditis, rheumatic fever, thyrotoxicosis or mesenchymoma. At the same time, early diagnosis followed by prompt surgical removal is mandatory to prevent mutilating or lethal complications of the tumor. Six cases of left atrial myxoma were diagnosed in our hospital during 1975-1978. We present the case histories, diagnostic findings and surgical findings, consolidating the role of echocardiography in detecting left atrial myxomas. We propose the use of echocardiography as a screening examination for atrial myxoma in the following settings: suspected mitral valve disease, suspected endocarditis with negative cultures, peripheral embolism or thrombosis in patients with unexplained cardiac failure and atrial myxoma with uncharacteristic presentation.

*Key words:* left atrial myxoma, differential diagnosis, echocardiography, screening.  
Acta Med Scand 206 115-121 1979

Left atrial myxomas are known for their masquerading features, presenting with obstructive, embolic or constitutional symptoms in varying combinations (5). Apart from mitral stenosis and aortic regurgitation, diagnoses like endocarditis, rheumatic fever, mesenchymoma and cardiomyopathy are frequently suspected before a definitive diagnosis of left atrial myxoma is established by catheterization or operation (9, 13, 14, 18, 25). The early reports documenting the feasibility of echocardiographic detection of left atrial myxoma (1, 2). Effert and Domanig (2) in Germany and (1) and later Holm and Henningsen (10) in Norway. In more recent papers have appeared recommending echocardiography as a valuable

screening procedure in this setting (4, 15, 22, 26, 27).

During the last 2½ years we have diagnosed six cases of left atrial myxoma. We report the clinical features and diagnostic procedures regarding these cases with the aim of consolidating the role of echocardiography as a unique screening procedure prompting early detection and treatment of myxomas.

## PATIENTS

From Sept. 1975 to April 1978, six patients were operated on in our hospital for left atrial myxoma. Age, sex, clinical and laboratory data are summarized in Table I. Only one patient (no. 4) was suspected of a left atrial myxoma on clinical grounds alone. Clinical suspicions precipitating pre-catheterization referral to ultrasound examinations are shown in Table II. One patient (no. 1) however was not examined by echocardiography.

## CASE REPORTS

### Patient 1

A 55-year-old woman with a history of previous rheumatic fever and dyspnea on effort. The characteristic findings of mitral stenosis and regurgitation were noticed on physical examination (Table I). The diagnosis was confirmed at right and retrograde left heart catheterization with left ventricular angiography. Echocardiography was not available at the time of initial diagnosis. Before the scheduled operation the patient was readmitted with symptoms of increasing dyspnea and fever. Hyperkalemia and anemia were now present. Shortly before and during this admission the patient experienced several syncope. A diagnosis of recurrent rheumatic fever or endocarditis was suspected and the patient was treated with penicillin despite negative blood cultures. At operation a 3×4×5 cm pedunculated left atrial myxoma was found. The postoperative course was uneventful. In retrospect the myxoma in the left atrium was faintly seen on the left ventricular angiogram.

Table I Clinical and laboratory findings in 6 patients with left atrial myxoma

All patients had sinus rhythm

DM = diastolic murmur SM = systolic murmur S<sub>1</sub> & S<sub>2</sub> = first and second heart sounds Hb = blood hemoglobin concentration SR = sedimentation rate

Pat no	Sex	Age (y)	Presenting symptoms	Auscultation	Pertinent laboratory
1	♀	55	Dyspnea fever syncope	Accentuated S <sub>1</sub> & S <sub>2</sub> opening snap SM & DM	Hb ↓ SR ↑ bk cultures neg
2	♂	42	Dyspnea fever fatigue loss of weight arthralgias palpitations	Accentuated S <sub>1</sub> & S <sub>2</sub> protodiastolic gallop DM	Hb ↓ SR ↑ ε γ-globulin ↑ cultures neg
3	♀	38	Dyspnea fever loss of weight	Accentuated S <sub>1</sub> & S <sub>2</sub> protodiastolic gallop SM	Hb ↓ SR ↑ ε γ-globulin → cultures neg
4	♂	32	Recurrent arterial embolism (cerebrum retina legs)	Normal sounds no murmur	Hb → SR →
5	♂	61	Relentlessly progressing refractory heart failure fever	Tachycardia friction rub no murmur	Hb → SR →
6	♂	52	Dyspnea fever arthralgias exertional dizziness	Accentuated S <sub>1</sub> & S <sub>2</sub> inconstant DM no gallop	Hb → SR ↑ ε γ-globulin → cultures neg

*Patient 2*

A 42 year-old man with a one year history of increasing dyspnea, loss of weight, fatigue, arthralgias and fever. Accentuated first and second heart sounds were heard on auscultation. A protodiastolic gallop was present. The laboratory findings were compatible with a diagnosis of endocarditis, but blood cultures were negative (Table I). The patient was referred to echocardiography suspected of cardiomyopathy. The examination showed the presence of a left atrial myxoma. This finding was confirmed by heart catheterization with pulmonary angiography. At operation a 6×6×6 cm pedunculated myxoma was removed. The postoperative course was uneventful.

*Patient 3*

A 38-year-old woman with symptoms of cough, dyspnea and loss of weight progressing over half a year. At the time of initial admission to a local hospital she presented with fever and peripheral edemas. The patient was in sinus rhythm. First and second heart sounds were accentuated. A grade 3/6 holosystolic murmur and a protodiastolic gallop were heard at the apex. Anemia and hypersedimentation were present (Table I). Blood cultures were negative. Mesenchymosis, endocarditis, myocarditis, mitral stenosis and atrial septal defect were all suspected by different examiners. In view of the equivocal findings the patient was referred to our laboratory for echocardiographic examination. The diagnosis of left atrial myxoma was established by ultrasound (Fig. 2) and confirmed by pulmonary angiography. At operation a 3×3×5 cm pedunculated myxoma was found. The postoperative course was uncomplicated.

*Patient 4*

A 32 year-old man with recurrent arterial embolism during 2½ years. Suspected of increased thrombocyte aggrega-

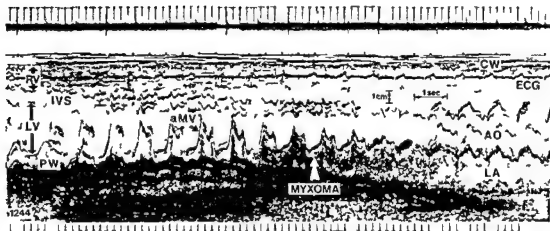
tion the patient was treated with anticoagulation. From embolism there had been neither systemic manifestations (Table I). Phlebography, chest X-ray and laboratory data were normal. Nevertheless the multiple emboli which had left the patient with a slight loss of visual acuity of one eye, brought a left heart myxoma, and the patient was referred to echocardiography. The examination revealed a (2×2×3 cm) non-obstructing myxoma in the left atrium (Fig. 1). This finding was confirmed by pulmonary angiography and operation. The postoperative course was uneventful.

*Patient 5*

A 61 year-old man with relentlessly progressing refractory bilateral heart failure associated with digoxin and diuretics without improvement. A cardiologist at a late point of the course

Table II Suspected clinical diagnosis, echocardiographic examination or operation

	Pt
Mitral valve disease	1
Endocarditis	1
Myocarditis	2
Cardiomyopathy	2
Pericardial effusion	5
Atrial septal defect	3
Myxoma	4
Mesenchymosis	3
Pathological coagulation	4



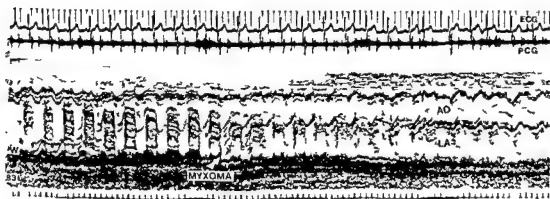
Representative M mode echocardiogram from patient 1 demonstrating a small sessile non-obstructing pedunculated myxoma. During recording the angulation of the transducer has been changed continuously in a direction through the inferior part of the left ventricle (LV) near the apex to a direction intersecting the heart represented by the aortic root (AO) left atrium (LA). Tumor echoes are seen in the

inferior part of the left atrium behind the anterior mitral leaflet (AMV) throughout systole and diastole but do not enter the left ventricle reflecting small excursions of a sessile tumor. The motion pattern of the anterior mitral leaflet is normal. CW = chest wall ECG = electrocardiogram IVS = interventricular septum PW = posterior wall RV = right ventricle.

severe distress. A regular tachycardia was present on auscultation and a friction rub was heard (Table 1). There was no effusion with cardiac compromise was suspected. The echocardiographic examination displayed a large myxoma in the left atrium (Fig. 3). Considerable poor condition of the patient, no angiograms were performed. At operation a huge (3.5 × 8 × 8 cm) pedunculated myxoma occupying the greater part of the left atrium and partially obstructing the pulmonary veins was removed. The postoperative course was uncomplicated.

#### Patient 6

A 52 year old man with a three year history of palpitations. Progressing dyspnea had developed over half a year. On heavy exertion the patient had experienced a few seconds of pronounced dizziness accompanied by temporary loss of vision. Proper syncope had not been present. During three months there had intermittently been episodes of fever and arthralgias. On admission the patient was in sinus rhythm and first and second heart sounds were accentuated. A diastolic rumble was heard incon-



M mode echocardiogram from patient 3 demonstrating a moderate sized myxoma. Recording obtained as follows: During systole tumor echoes are seen in the left atrium (LA) behind the inferior part of the aortic root. During diastole the tumor echoes are seen in the left atrium reflecting the swinging motion of the tumor. The motion of the anterior mitral leaflet is

abnormal showing flattened or diminished diastolic closing rate suggesting obstruction of the mitral orifice. The phonocardiogram (PCG) shows an early diastolic sound (tumor plop) occurring simultaneously with the maximal diastolic excursion of the myxoma. Abbreviations as in Fig. 1.





Fig 3 M mode echocardiogram demonstrating large obstructing myxoma in patient 5. Tumor echoes are seen throughout the cardiac cycles in the visible part of the left atrium (also above the level of the aortic valves) reflecting a large tumor characterized by small excursions. Only a minor part of the tumor is seen in the mitral ostium

during diastole. The diminished mitral valve excursion, the enlarged left atrium, the small excursions of root and the very short ejection time as seen on aortic valve echogram signify severe obstruction of the mitral orifice associated with low stroke volume. Abbreviations as in Fig 1.

sistently at the apex but no gallop was noticed. Slight hypersedimentation was present while all other laboratory tests were normal (Table I). Suspected of mitral valve disease, the patient was referred for echocardiography which revealed a large mass occupying the visible part of the left atrium. Pulmonary angiography confirmed the echocardiographic finding. At operation a myxoma was successfully removed, the tumor being ellipsoid (5x5x6 cm) and attached by a 3 cm broad base to the interatrial septum and prolapsing only partly through the mitral orifice. The postoperative course was uncomplicated.

### DIAGNOSTIC METHODS

M mode echocardiography was performed using an Echoscan 30 equipment (Mediscan, Denmark) with a 2.25 MHz transducer with 7.5 cm focus. Recordings were obtained by means of a Cambridge Multichannel Physiological Recorder using photographic paper (Kodak Linagraph 1930). Several scannings from the left ventricle to the base of the heart or vice versa were obtained according to Feigenbaum (3). Care was taken to visualize the left atrium, the mitral valve region and the left ventricle to obtain information on tumor extension, mobility and degree of obstruction of the mitral ostium. Patient 1 was not examined by echocardiography.

#### Catheterization and angiography

Right and retrograde left heart catheterization with left ventricular angiography in 30° RAO (Urografin® 76%) were performed in patient 1. Patients 2-6 were examined by right heart catheterization only, since the presence of a left atrial mass had been shown by echocardiography. Pulmonary angiography (Urografin® 76%) in 30° RAO was performed in these patients. This procedure was however omitted in patient 5 due to severe pulmonary hypertension and poor clinical condition.

### RESULTS OF DIAGNOSTIC METHODS

The diagnosis of left atrial myxoma was established (patients 2-6) or established (patient 1) before heart surgery. Five patients (nos. 2-6) were examined by echocardiography prior to catheterization. operation were all unequivocally diagnosed as having left atrial myxomas. They were all operated upon within a few days after the ultrasonic diagnosis before further complications occurred.

No false positive diagnosis of myxoma was made in the department during the period. In one patient (no. 1) a false negative echocardiographic study was performed. The echocardiographic patterns of tumor localization, obstruction of aortic root and mitral valve movements were consistent with the findings of tumor localization and movements as evaluated by catheterization, angiography or operation (Table III).

Figs 1, 2 and 3 respectively show the echocardiographic patterns of a small non-obstructing, non-prolapsing tumor of a medium-sized obstructing and prolapsing tumor and finally a large tumor almost occluding the left atrium and protruding into the left ventricle during diastole.

### DISCUSSION

Despite their benign histological appearance, myxomas usually induce a malignant disease characterized by progressing refractory cardiac failure, embolizing or lethal embolism or sudden death.

### III Echocardiographic, angiocardigraphic and surgical findings

trial valve EF slope (diastolic closing rate of mitral valve) LA =left atrium LV=left ventricle MO=mitral orifice

Echocardiography	Angiocardigraphy	Surgery
Not performed	Left ventricular angiography mitral stenosis and incompetence (in retrospect prolapsing pedunculated tumor)	3×4×5 cm pedunculated tumor
EF<10 mm/sec systole tumor in LA diastole tumor in LV	Pulmonary angiography prolapsing pedunculated tumor	6×6×6 cm pedunculated tumor
EF<10 mm/sec systole tumor in LA diastole tumor in LV	Pulmonary angiography prolapsing pedunculated tumor	3×3×5 cm pedunculated tumor
EF>10 mm/sec systole tumor in LA diastole tumor in LA	Pulmonary angiography non prolapsing sessile tumor	2×2×3 cm sessile tumor
EF<10 mm/sec systole tumor in LA diastole tumor in LA & LV	Not performed	3.5×8×8 cm pedunculated tumor obstructing pulmo nary veins
EF<10 mm/sec systole tumor in LA diastole tumor in LA & MO	Pulmonary angiography sessile tumor prolapsing partly through MO	5×5×6 cm sessile tumor

Early surgical removal of the tumor carries an  
 nt prognosis and therefore early diagnosis  
 atment are mandatory  
 ptoms and signs are frequently suggestive  
 tually never diagnostic. Due to the rarity of  
 as and the highly variable clinical picture  
 ommon cardiac diseases are usually sus  
 Obstruction of the mitral ostium—the most  
 n manifestation of left atrial myxoma—will  
 be misdiagnosed as rheumatic mitral stenosis  
 8 9 14 18). The combination of sinus  
 a short history of symptoms and a negative  
 of rheumatic disease however should sug  
 e possibility of myxoma (9). All our patients  
 n sinus rhythm and with two exceptions (pa  
 4 and 6) the history was less than 1 year  
 ng spells or endocarditis like symptoms  
 further support a suspicion of myxoma (pa  
 ) Arterial embolism may be the only manifes  
 of a left sided myxoma (patient 4) and histo  
 examination of peripheral emboli removed  
 surgery may occasionally be diagnostic (11)  
 presence of a pedunculated prolapsing left  
 tumor swinging between the left atrium and  
 ventricle is usually associated with a loud  
 nged and delayed first heart sound at the time

of ejection of tumor from the left ventricle to the left  
 atrium and an early diastolic sound or protodiastolic  
 gallop at the time of maximal prolapse of the tumor  
 into the left ventricle (Fig. 2) (12). Variable systolic  
 and diastolic murmurs are heard depending on the  
 degree of mitral regurgitation or obstruction of the  
 mitral ostium. When pulmonary hypertension de  
 velops the pulmonary component of the second  
 heart sound becomes accentuated. The auscultato  
 ry findings are often indistinguishable from those of  
 rheumatic valvular disease. However murmurs  
 changing with position, apparent late opening snap  
 despite severe obstructive symptoms and low fre  
 quency indistinct character of the opening snap  
 ( tumor plop ) are auscultatory features of potential  
 help in differentiating mitral stenosis from left atrial  
 myxoma (15).

In our cases auscultation appeared to be of lim  
 ited value (Table II). Furthermore patients with  
 myxomas need not at all have murmurs if stroke  
 volume is very low (patient 5) or if tumor is very  
 small and non-obstructing (patient 4). Prolapsing  
 highly mobile tumors were characteristically asso  
 ciated with increased first heart sounds and early  
 diastolic gallop in our series (patients 1 2 3). The  
 degree of prolapse seems to be dictated not only by

the length of the pedicle by which the tumor is attached to the atrial wall, but also by the size shape and consistency of the tumor. In patients 4 and 6 the tumor mobility was limited by a short and broad stalk. In patient 5 the tumor though pedunculated was impacted between the walls of the atrium and thereby restricted in motion. The small and slow excursion of the tumors in these patients may explain the absence of an audible tumor plop.

The combination of a cardiac murmur and continuous fever with or without concurrent arterial embolism—often arouse suspicion of infectious endocarditis. This diagnosis may be supported by laboratory evidence of anemia, elevated sedimentation rate or changes in the concentrations of serum proteins as seen in our patients 1, 2 and 3. Positive blood cultures do not exclude myxoma, since left atrial myxomas may become infected (24). Even clubbing can be a sign of both endocarditis and myxomas (5, 6, 8, 15, 16, 26). In this setting an echocardiogram can be of great help, since scanning of the valves usually will distinguish between myxoma and valvular lesions due to the vegetations (3), although mitral fungal vegetations in rare cases can be sufficiently large to mimic the echocardiographic picture of a left atrial myxoma (17).

When hypersedimentation, anemia and hyperglobulinemia occur associated with fever, loss of weight, Raynaud's phenomenon or joint pains, the primary significance of cardiac manifestations may be neglected and a diagnosis of mesenchymosis or rheumatic fever consequently suspected (patient 3) (7, 13, 25). Likewise, the combination of cardiac signs and symptoms and constitutional manifestations may suggest a diagnosis of myocarditis or cardiomyopathy (patients 2, 3) (21).

Occasionally the only obvious manifestation of a left atrial myxoma may be severe heart failure. The absence of heart murmurs in that setting is probably due to low cardiac output (patient 5) (21, 23).

Correct diagnosis will usually be made by means of catheterization and angiography (Table III). However, the diagnosis may be missed if a left atrial myxoma is not specifically suspected, as seen in one of our patients (no. 1) and previously reported by others (15). Furthermore, left sided heart catheterization and particularly transseptal puncture is associated with risk of tumor fragmentation and embolism (14, 19). Hemodynamic features of left atrial myxomas are variable. Prolapsing tumors may be associated with increased  $c$  and  $v$  waves

followed by rapid  $y$ -descents although mitral insufficiency is present (16, 20). These changes were seen in three of our patients (2, 3) having highly mobile tumors but little regurgitation. Obviously pressure tracing specificity in diagnosing myxomas.

Although the echocardiographic findings of atrial myxoma represent a spectrum, the pictures are seen reflecting tumor size and position (Figs 1, 2, 3, Table III). The echocardiogram of patient 4 shows a small tumor (Fig. 1) located in the left atrium behind the anterior valve throughout systole and diastole but not the left ventricle. The diastolic movement of the anterior mitral valve is normal, indicating that the tumor does not obstruct the mitral orifice. In accordance with this, angiography and surgery demonstrated a sessile, non-prolapsing, non-obstructing small myxoma attached to the low  $c$  septum.

The echocardiograms from patients 2 and 3 show the pattern of a moderate sized prolapsing tumor (Fig. 2). Echoes are seen in the left atrium and in the left ventricular inflow tract during diastole, thus suggesting the swinging motion of the tumor (Table III). The diastolic closing of the anterior mitral leaflet is reduced, reflecting the obstruction of the mitral orifice. Moderate sized prolapsing highly mobile tumors were found at angiography and operation (Table III). The echocardiograms from patients 5 and 6 show very large tumors occupying the visible part of the left atrium. Tumor echoes are seen in the left atrium throughout systole and diastole, reflecting the small size of the myxomas. Furthermore, only during diastole the tumor are seen within the mitral funnel. At surgery a large sessile tumor was found in patient 6, while in patient 5 the tumor was pedunculated, appeared to be restricted in motion due to the size of the myxoma (Table III).

Apart from the horizontal diastolic closure of the mitral valve, associated echocardiographic findings in patient 5 were poor excursion of the aortic root and a very short ejection time from the aortic valve. Echocardiogram signs of severely depressed stroke volume were confirmed at catheterization. At surgery the large tumor impacted in the left atrium was found to obstruct not only the mitral orifice but also the entrance of more of the pulmonary veins.

Thus, regular correlations between echocardiographic and surgical findings are

c and hemodynamic/angiographic and surgical findings obviously exist. Based on our experience and on previously published evidence we think that systematic echocardiographic screening for left atrial myxoma should be performed in following settings: 1) Suspected mitral obstruction 2) Suspected endocarditis with negative blood cultures 3) Peripheral embolism or infarction in young patients 4) Unexplained heart failure 5) Mesenchymal mass with uncharacteristic presentation. Echocardiographic screening according to these guidelines will secure correct diagnosis and treatment, thus preventing the serious complications of undiagnosed mass.

# REFERENCES

1. Lerner I. Personal communication.
2. Lerner S & Domanig E. Diagnostik intraaunkularer Thromben und grosser Thromben mit dem Ultraschall. *Echoverfahren Dtsch Med Wochenschr* 84: 619-624 1979.
3. Feigenbaum H. *Echocardiography*. 2nd ed. Lea & Febiger, Philadelphia 1976.
4. Tegan R E & Harrison D C. Diagnosis of left atrial myxoma by echocardiography. *N Engl J Med* 281: 1022 1970.
5. Redwin J F. Diagnosis of left atrial myxoma. *Lancet* i: 464 1963.
6. Penwood W F. Profile of atrial myxoma. *Am J Cardiol* 21: 367 1968.
7. Gustafson A G, Edler I G & Dahlback O K. Bilateral atrial myxomas diagnosed by echocardiography. *Acta Med Scand* 201: 391 1977.
8. Lawrence W P. Clinical aspects of cardiac tumors. *N J Cardiol* 21: 328 1968.
9. Lofors E & Mogensen L. Atrial myxoma: 12 cases operated in Stockholm 1954-1973. *Eur J Cardiol* 10: 174 1974.
10. Olsson H H & Henningsen P. Ekkokardiografi. *Läkarskrift* 129: 1710 1967.
11. Nikkilahti K, Koskinen S & Luosto R. Left atrial myxoma revealed by femoral embolectomy and J Thorac Cardiovasc Surg 11: 33 1977.
12. Matham A. Auscultation of the heart and phonocardiography. 2nd ed. Churchill Livingstone, London 1975.
13. Lortscher R H, Towes W H, Nora J J, Wolf R R & Spangler R D. Left atrial myxoma presenting as rheumatic fever. *Chest* 66: 402 1974.
14. Marpole D G F, Kloster F E, Brinstow J D & Griswold H E. Atrial myxoma: a continuing diagnostic challenge. *Am J Cardiol* 23: 597 1969.
15. Nasser W A, Davis R H, Dillon J C, Tavel M, Helmen C H, Feigenbaum H & Fisch C. Atrial myxoma: Phonocardiographic, echocardiographic, hemodynamic and angiographic features in nine cases. *Am Heart J* 83: 810 1972.
16. Ognibene J A & Nelson W P. Atrial myxoma: Comments on hemodynamic alterations. *Dis Chest* 52: 699 1967.
17. Pasternak R C, Cannon D S & Cohen L S. Echocardiographic diagnosis of large fungal verruca attached to mitral valve. *Br Heart J* 38: 1209 1976.
18. Peters M N, Hall R J, Cooley D A, Leachman R D & Garcia E. The clinical syndrome of atrial myxoma. *JAMA* 230: 695 1974.
19. Pinduck F, Rierce E C, Baron M G & Lukban S B. Embolization of left atrial myxoma after trans septal cardiac catheterization. *Am J Cardiol* 30: 569 1972.
20. Pitt A, Pitt B, Schaefer J & Criley J M. Myxoma of the left atrium: Hemodynamic and phonocardiographic consequences of sudden tumor movement. *Circulation* 36: 408 1967.
21. Popp L R & Levine R. Left atrial mass simulating cardiomyopathy. *J Clin Ultrasound* 1: 96 1973.
22. Potts J L, Johnson L W, Eich R H, Fruehan C T & Obaid A I. Varied manifestations of left atrial myxoma and the relationship of echocardiographic patterns of tumor size. *Chest* 68: 781 1975.
23. Rae A. Two patients with cardiac myxoma: one presenting as bacterial endocarditis and one as congestive cardiac failure. *Postgrad Med J* 41: 644 1965.
24. Rogers E W, Weyman A E, Noble R J & Bruins S C. Left atrial myxoma infected with histoplasma capsulatum. *Am J Med* 64: 683 1978.
25. Skanse B, Berg N O & Westfelt L. Atrial myxoma with Raynaud's phenomenon as the initial symptom. *Acta Med Scand* 164: 321 1959.
26. Sparvieri F, Sgarbi E & Massini C. La diagnosi ecocardiografica di mixoma dell'atrio sinistro. *G Ital Cardiol* 6: 849 1977.
27. Terdjman M, Richard D, Magnier S, Gay J, Scebat L, Gerbaux A & Pernod J. Diagnostic des myxomes de l'oreillette gauche par échographie ultrasonore. *Arch Mal Coeur* 69: 1145 1976.



# Massive Embolization of Cardiac Myxoma

## A Case Report

Gunnar Tornvall and Christian Olin

*From the Medical Department Sabbatsberg's Hospital and the Thoracic Surgical Clinic Karolinska Hospital Stockholm Sweden*

**ABSTRACT** A case of left atrial myxoma with massive embolization in a 20-year-old woman is described. The initial clinical picture was confusing but repeated examinations including enzyme determinations and arteriographies disclosed the presence of multiple arterial emboli. At embolectomy, histological investigation of embolic masses showed a picture suggesting cardiac myxoma. This diagnosis was confirmed by pulmonary angiography and the tumour removed. Postischaemic oedema of the legs necessitated decompression operations. The peripheral circulation was restored and the final result was excellent. Some aspects of the clinical presentation of this uncommon disease are discussed.

**Keywords:** cardiac myxoma, arterial embolization, postischaemic oedema, fasciotomy.  
Med Scand 206 123 1979

Cardiac myxoma is a rare tumour that occasionally cause dramatic and confusing symptoms. We recently experienced a case of left atrial myxoma in a young woman presenting with leg cramps and subsequently offering some unusual problems regarding both diagnosis and treatment.

### CASE REPORT

A previously healthy 20-year-old woman was suddenly ill with bilateral leg cramps while swimming. As the cramps were quite severe and persistent, she was brought to hospital without delay. On admission to Sabbatsberg's Hospital on the evening of July 25th 1976, she complained of painful muscular cramps in both legs and coldness in the feet. On examination, however, the dorsal arterial pulses were palpable on both sides and the temperature of the feet did not differ. Physical examination of the legs was normal and the BP was 100/90 mmHg. Laboratory investigation revealed low levels of serum sodium (135 mmol/l) and serum potassium (2.8 mmol/l). As the patient had been standing in the sun all day—one of the hottest during that summer—a salt depletion syndrome (miner's cramps) was suspected. She was ac-

cordingly treated with salt and fluid replacement, but in spite of normalization of the electrolyte values the painful cramps persisted and she required repeated doses of sedatives and analgesics.

During the following hours her condition deteriorated. She complained of abdominal cramps, nausea and vomiting. An abdominal radiographic examination was negative. Six hours after admission, red urine was noted and was shown by laboratory analysis to be caused by myoglobin. Furthermore, CPK and liver enzymes (ASAT and ALAT) were greatly elevated. A repeat examination of the legs now disclosed that the circulation in the left leg had deteriorated and that the pulse of the left femoral artery could no longer be palpated. An arteriography was immediately performed, showing a total occlusion of the left external iliac artery and some smaller contrast defects in other vessels (Fig. 1).

The patient was referred to the Thoracic Surgical Clinic on the evening of July 26 for further treatment. On admission, she still complained of pain in both legs. The muscular cramps were less pronounced. The left leg was pale and cold below the middle of the thigh and she was not able to move the lower leg. The right foot was also somewhat cold but no severe circulatory disturbance was present on that side. Chest X ray and ECG were normal.

An acute embolectomy was immediately performed and through an incision in the left femoral artery, large amounts of red yellowish thrombus could be extracted both proximally and peripherally with the aid of a Fogarty catheter. The specimen was sent for microscopic investigation. After completion of the embolectomy, a blood flow of 300 ml/min was measured in the femoral artery and the foot immediately became red and warm.

Some hours after operation the left leg started to swell due to a diffuse oedema in the previously ischaemic musculature. Eight hours after the embolectomy the lower leg was so intensively swollen that the venous circulation began to be compromised. To prevent further deterioration of the circulation and in order to decompress the calf muscles that were in immediate danger of pressure necrosis, a fasciotomy operation had to be performed. The oedematous muscles literally bulged out through the incision, leaving a 15 cm diastasis between the skin edges.

In the meantime the right foot had begun to be ischaemic and an attempt was made to perform an embolectomy on the right leg. Even though the embolectomy catheter could be passed all the way down to the foot, no



Fig 1 Angiogram showing complete occlusion of left external iliac artery

embolic material could be retrieved. A new arteriography was therefore performed on the right leg and showed a subtotal occlusion of the popliteal artery immediately above the knee. A repeat embolectomy (this time through the right popliteal artery) was performed and an embolus that was partly attached to the vessel wall could be extracted with the aid of a Fogarty catheter. In addition some fresh thrombotic material could be removed from the distal arteries of the leg. The right foot immediately became warm and distant pulses could be palpated. Following the operation however the same thing happened as on the left side, namely the right lower leg became swollen due to the postischaemic oedema that a fasciotomy procedure had to be carried out on this side as well.

At this stage the general condition of the patient was markedly affected. Due to renal damage by myoglobin precipitation and to the repeated operations and blood transfusions the kidneys started to fail. Serum creatinine was above 600 mmol/l. Fluid accumulated in the lungs but the condition could be controlled with intermittent respirator treatment and large doses of furosemide.

The result of the microscopic examination of the emboli was available on the sixth day after the first embolectomy. A strong suspicion of cells originating from a cardiac myxoma was at hand. This finding motivated an angiographic examination of the heart. A pulmonary angiogram was performed and a 4x6 cm large contrast defect was seen in the left atrium suggesting the presence of a pedunculated myxoma. On the night after the investigation the patient experienced a sudden thrust of pain in the right hypocondrium suggesting an embolus to the liver. It was decided not to wait with removal of the myxoma.

On the next day (Aug 4) the operation was performed through a median sternotomy and with the aid of extracorporeal circulation and temporary cardiac arrest. The friable myxoma together with its attachment on the base of the interatrial septum could be removed (in one piece)

without problems (Fig 2). Except for postoperative bleeding which necessitated re-operation the postoperative course was uneventful and the patient made a very rapid recovery. The kidney function returned to normal within a week.

Rehabilitation was for natural reasons hampered by large open wounds on both lower legs. A skin transplant was suggested by the plastic surgeons but had to be postponed due to a wound infection. The swollen calf muscles had in the meantime diminished and after a week's daily application of wound tape the incision from the fasciotomy could be closed by direct suture on both sides, leaving a very satisfactory cosmetic result. An active mobilization program could now be started. After about a month the patient was able to walk. At a follow-up examination in Jan 1977 she could walk without problems and had resumed work. The left leg was slightly thinner than the right and some reduction in muscular strength was evident. Circulation was normal on both legs.

Rehabilitation was for natural reasons hampered by large open wounds on both lower legs. A skin transplant was suggested by the plastic surgeons but had to be postponed due to a wound infection. The swollen calf muscles had in the meantime diminished and after a week's daily application of wound tape the incision from the fasciotomy could be closed by direct suture on both sides, leaving a very satisfactory cosmetic result. An active mobilization program could now be started. After about a month the patient was able to walk. At a follow-up examination in Jan 1977 she could walk without problems and had resumed work. The left leg was slightly thinner than the right and some reduction in muscular strength was evident. Circulation was normal on both legs.

## COMMENTS

Peripheral arterial embolism in a previously healthy young individual is a rare occurrence. Amongst the conditions reported to cause arterial emboli, the following people may be mentioned: bacterial endocarditis, mitral valve disease with atrial fibrillation, certain uncommon coagulation disorders, and trauma. In these conditions could be demonstrated in the patient. She had no history of fever, cardiac or coagulation problems. The heart was normal on auscultation, ECG and chest X-ray. The dis-



Fig 2 The removed myxoma with its attachment to the interatrial septum

sis was obtained through microscopic examination of the embolic material from the legs. The massive nature of the embolization was seen. Atrial myxoma was considered a possibility although her age and the absence of cardiac symptoms spoke against this diagnosis.

The initial clinical picture with bilateral severe cramps was most confusing. The pronounced muscular cramps can be explained by the fact that embolization took place during exercise (swim) and that the response of the musculature to an ischaemia is probably different during exertion and at rest.

The electrolyte disturbance that is found on admission may also have contributed to the altered reaction. The gradual deterioration of the arterial circulation is explained by secondary thrombosis distal to the emboli. The muscular ischaemia became finally so pronounced as to cause release of myoglobin and enzymes.

Approximately 40% of patients with left atrial myxoma have peripheral embolization of tumour fragments. (4) Almost all organs have been reported to be a site of emboli (9-17). Cerebral emboli are common and fatal outcome has been reported (3).

Most patients with left atrial myxoma have cardiac symptoms due to obstruction of the mitral orifice. A myxoma usually originates from the lower part of the interatrial septum and is pedunculated. When the myxoma has reached a certain size it will obstruct the mitral valve during diastole and will in many cases simulate mitral stenosis (6).

The tumour is not detected until an operation for a suspected mitral stenosis is undertaken (11-13). Constitutional symptoms such as fever, malaise, weight loss and high ESR are reported to occur in 90% of the cases but these findings are uncommon and difficult to interpret (5).

Echocardiography is of great value in the diagnosis of cardiac myxoma. At the time in question this diagnostic aid was not available at our institutions. It should also be born in mind that cases have been reported in which the myxoma has been small and located in the left ventricle and might thus have been overlooked at an echocardiographic examination focused on the atria (1). Therefore an angiographic examination is usually necessary and the

best way is to perform a pulmonary angiogram. When the myxoma will appear as a mobile contrast filling defect when the contrast medium has reached the pulmonary artery.

In our patient the postischaemic oedema was so

severe that a bilateral fasciotomy had to be performed. Had this not been done further muscular damage would probably have taken place. Fortunately the muscular swelling soon diminished rendering skin transplantation unnecessary and an excellent cosmetic result was obtained after direct wound closure. The patient is now back in her previous occupation as a swimming teacher and has only a slight reduction of the muscular strength in her left leg.

Atrial myxoma is generally considered to be a benign tumour although the tendency to obstruct the mitral valve and to embolize makes it clinically malignant. Recurrence is very rare and is probably due to incomplete removal of the tumour (16). Follow up examination including echocardiography is however warranted.

## REFERENCES

- 1 Björk V O & Björk L. Left ventricular myxoma. *Thorax* 6: 534 1965.
- 2 Crafoord C. Panel discussion on late results of mitral commissurotomy. In: *International Symposium in Cardiovascular Surgery. Studies in physiology, diagnosis and techniques* (ed C R Lamb) p 202. Saunders Philadelphia 1955.
- 3 Floderus S & Hedenstedt S. Endocardomyxoma två fall med emboli. *Läkartidningen* 52: 3931 1968.
- 4 Goodwin J F. Diagnosis of the left atrial myxoma. *Lancet* i: 464 1963.
- 5 — The spectrum of cardiac tumors. *Am J Cardiol* 21: 307 1968.
- 6 Hedfors E & Mogensen L. Atrial myxoma 12 cases operated in Stockholm 1954-1973. *Eur J Cardiol* 2/1: 101 1974.
- 7 Khan M S R & Mujahed M A. Atrial myxoma producing a saddle embolus in a child. *Thorax* 25: 634 1970.
- 8 Koikkalainen K, Kostainen S & Luosto R. Left atrial myxoma revealed by femoral embolectomy. A case report and review of the literature. *Scand J Thorac Cardiovasc Surg* 11: 33 1977.
- 9 Kulkarni M, Jessiman J M & French S. Entire left atrial myxoma presenting as a saddle embolus. *Thorax* 24: 629 1969.
- 10 Larmi T K, Järvelin J, Karkola P, Kariluoma M J & Takkunen J. Surgical treatment of cardiac myxoma. A case report. *Ann Chir Gynaecol* 66: 18 1977.
- 11 Marpole D G F, Kloster F E, Brinstow J D & Griswold H E. Atrial myxoma: a continuing diagnostic challenge. *Am J Cardiol* 23: 597 1969.
- 12 Mundth E D, Wheeler E O, Moses J M & Austen W G. Clinical aspects of left atrial myxoma. Report of a case simulating subacute bacterial endocarditis and review of five cases treated surgically. *Ann Thorac Surg* 5: 1968.



- 13 Neilson G H Experiences with left atrial myxoma Aust Ann Med 17 38 1968
- 14 Peters M N Hall R J Cooley D A Leachman R D & Garcia E The clinical syndrome of atrial myxoma JAMA 5 695 1974
- 15 Prichard P W Tumours of the heart Review of subject and report of one hundred and fifty cases Arch Pathol 51 98 1951
- 16 Read R C White H J Murphy M L & D Sun C N & Flanagan W H Malignancy of left atrial myxoma J Thorac Cardiovasc 68 857 1974
- 17 Silverman J Olwin J S & Greatinges J S Atrial myxomas with systemic embolization. Literature and report of a case Circulation 1962

# Diastolic Wave Initiating Ventricular Tachyarrhythmias and Suppressible by Lignocaine and Isoprenaline

Erik Orinius

*From the Division of Cardiology, Department of Medicine, Thoracic Clinics, Karolinska Hospital, Stockholm, Sweden*

**FACT** A patient is described with ventricular tachycardia and premature beats (VPB) probably initiated by a diastolic wave, which—like the VPBs—can be eliminated by lignocaine and isoprenaline

*Key words:* ventricular tachycardia, prolonged Q-T interval, premature beats, wave alternans

Acta Med Scand 206 127-129 1979

Prolonged Q-T interval and alternating T waves are often associated with paroxysmal ventricular tachycardia and ventricular fibrillation (VF) but the arrhythmias are not so frequent that the mere finding of a prolonged Q-T interval or alternating T waves warrants acute VT/VF prophylaxis. A more specific warning sign has been described in patients with a prolonged Q-T interval during quinidine treatment (1). It is a diastolic wave that cannot be seen on U in a strict sense. It nearly always ends with a ventricular premature beat (VPB) and such an episode of VT/VF by minutes-hours in 9 of 10 patients in that series. Another 23 of those 10 treated patients had prolonged Q-T interval without developing VT/VF and none of them showed the diastolic wave.

This report concerns a patient without quinidine treatment who demonstrates that the diastolic wave following a VPB could be eliminated by lignocaine and isoprenaline while the Q-T interval remained prolonged.

## CASE REPORT

A 60-year-old girl was admitted acutely for a preoperative investigation during treatment of septicemia. She had to have a severe aortic incompetence and an aneurysm of the right sinus Valsalva with rupture into the right ventricle. ECG was normal 10 days before the planned surgery. Digoxin intoxication is suspected and the medication was discontinued.

The serum concentration of digoxin analyzed on the next day was 3.3 nmol/l (therapeutic range 1.0-2.5). However, before that was known the patient developed an observed circulatory arrest. ECG, recorded after some minutes of resuscitation measures, showed asystole. The circulation could be restored but the patient had not regained consciousness when an acute operation was started. A Björk-Shiley valve prosthesis was inserted in aortic position and a small fistula from the right sinus of Valsalva to the right ventricle was closed. The procedure was uneventful.

On the next morning the patient was still unconscious. ECG did not show any Q-T prolongation and the patient was normokalemic. Some hours later—23 hours after the circulatory arrest—she developed a long VT which disappeared during external cardiac massage given because of low blood pressure.

The VT was of torsade de pointes type (Fig. 1). The patient had not been treated with quinidine or any similar drug, nor had any phenothiazine or derivatives been given.

When lignocaine treatment was started following the VT, the patient had VPBs in bigeminy or quadrigeminy which were preceded—most easily seen in lead III—by a remarkable T-Q wave appearing in a 2:1 or 4:1 pattern (Fig. 2). After 75 mg lignocaine i.v., both the diastolic waves and the VPBs disappeared, leaving the prolonged Q-T interval (Fig. 3).

When the lignocaine infusion rate was reduced on trial, the diastolic wave returned in a 2:1 pattern and as the dose was further reduced, even the VPBs reappeared in bigeminy. As the lignocaine dose was again increased both the diastolic waves and the VPBs disappeared.

Lignocaine treatment was discontinued after 8 hours. Five hours later, premature beats with aberrant ventricular conduction but normal QRS width appeared and as before they were preceded by a T-Q wave in a 2:1 pattern (Fig. 4). This time isoprenaline was given (0.5 µg/min) and both the diastolic waves and the VPBs disappeared (Fig. 5). The antiarrhythmic therapy was stopped about 12 hours later, i.e. 48 hours after the circulatory arrest. No more episodes of VPBs or VT occurred.

The patient made a complete physical and psychic recovery.

**Abbreviations:** VT = ventricular tachycardia, VF = ventricular fibrillation, VPB = ventricular premature beat.

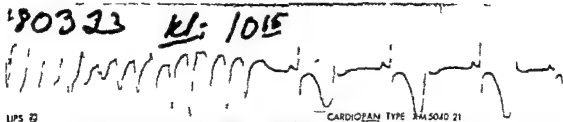


Fig 1 VT of torsade de pointe type 220/min followed by sinus rhythm with ventricular ectopic beats in

bigeminy Rhythm monitoring lead paper speed 25 sec

## COMMENTS

The ECGs in Figs 2 and 4 show Q-T prolongation alternating T waves and premature beats. Ventricular tachyarrhythmias are well known complications of prolonged Q-T interval (9) and in alternating T waves 4 out of 13 cases had also had VF (6). Closer examination of the ECG in Fig 4 reveals most clearly in lead III that the T wave after inscribing its vertex does not proceed downwards but turns into a wave (†) with greater amplitude than that of the T wave. It is slightly greater even if one subtracts the amplitude of the overlapping P wave so this cannot be called an U wave in a strict sense (5).

That this diastolic wave does not only precede but also initiates the VPBs is probable from Fig 2. The wave is easily seen in lead III (†) before each of the two VPBs. (What looks like a P wave just preceding the VPB is instead the last part of the diastolic wave and the first part of the VPB.) In contrast to QRS complex no 5 no 4 is preceded by a deeply negative T wave in leads I and II as are the VPBs but the T wave preceding QRS no 4 is not followed by a marked positive wave in lead III (‡). Extremity leads I II III. Paper speed 50 mm/sec.

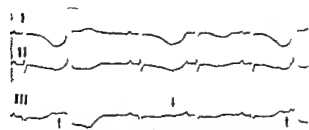


Fig 2 Sinus rhythm with VPBs preceded by a T-Q wave seen most easily in lead III (†). In contrast to QRS complex no 5 no 4 is preceded by a deeply inverted T wave in leads I and II as are the VPBs but the T wave preceding QRS no 4 is not followed by a marked positive wave in lead III (‡). Extremity leads I II III. Paper speed 50 mm/sec.

(the absence marked ‡). Therefore the wave probably initiates the VPBs.

The ECG in Fig 3 demonstrates that it could eliminate the diastolic waves and the T wave alternans. Evinsson (1) study whether lignocaine could eliminate diastolic waves and the following VPBs but it effective in preventing VT/VF during treatment.

Whether the premature beats in ECGs are ventricular or supraventricular cannot be without fusion beats. premature P waves. QRS duration is somewhat difficult to measure is probably not more than 0.09 sec. E premature beats do look rather like the complexes in lead II they differ strikingly. These premature beats might thus be of origin.

ECG no 5 demonstrates that both the waves and the premature beats disappear after isoprenaline infusion. Isoprenaline has been shown to abolish primary T wave abnormalities in contrast to epinephrine—not to trigger VT in patient with familial long Q-T syndrome and cerebral brain damage after a prolonged anoxic arrest (2).

The practical consequence of this is that VT preceded by diastolic waves can be treated.

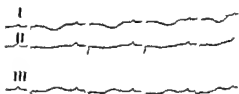


Fig 3 The same leads as in Fig 2 about 18 sec during lignocaine treatment. The T-Q wave is visible. VPBs have disappeared. Paper speed 50 mm/sec.

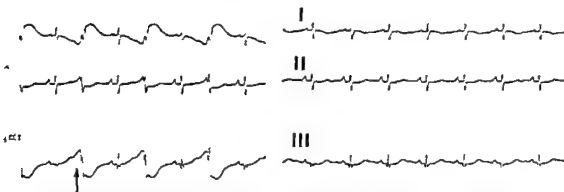


Fig 5 The same leads as in Fig 4 following 20 min of isoprenaline therapy. The T-Q wave and the ectopic beats have disappeared. Paper speed 25 mm/sec

sinus rhythm with ectopic beats in bigeminy. When the apex of a sinus beat has inscribed its vertex—most often in lead III—it does not proceed downwards but into a T-Q wave (†) with greater amplitude than that wave. It is slightly greater even if one subtracts the amplitude of the overlapping P wave and so it is not an extremity lead. I II III Paper speed 25 mm/sec

It would be ideal that this probably should be done as a baseline against VT/VF. Lignocaine is probably the best drug.

We can only speculate about the genesis of the T-Q waves and the ventricular tachyarrhythmias and how lignocaine and isoprenaline affect some ECGs reproduced in articles about long QT syndrome and alternating T waves show the T-Q wave (6, 7) but the present patient did not have any previous history corresponding to those arrhythmias. Nor had she been treated with quinidine, phenothiazine or derivatives. In Ejvinsson's study (1) all patients were or had been on digoxin some days before the start of quinidine treatment and the appearance of VT/VF and it might be on the basis of quinidine syncope is digitalis. The patient was treated with digoxin to a slightly serum concentration and this might have contributed to the tachyarrhythmias. The patient had symptoms of brain damage during a week or so during the circulatory arrest prior to surgery and cerebral disorders have been described to be associated with deeply inverted widened T waves and prominent U waves but not ventricular tachyarrhythmias (4). However if the brain is the tissue where digitalis induces ventricular tachyarrhythmias the anoxic damage might have released a mechanism in the present case.

Recently monophasic action potentials in patients with long Q-T syndrome have been shown to have an intermittent second deflection (3). This deflection may constitute the diastolic wave in the surface ECG of the present patient.

## REFERENCES

1. Ejvinsson T. Kindinsyncope p 101. Thesis Stockholm 1978.
2. Garza L A, McNamara D G, Nora J J, Vick R L & Sommerville R J. Familial repolarization myocardialopathy. *Am J Cardiol* 23: 112, 1969.
3. Gavrilescu S & Luca C. Right ventricular monophasic action potentials in patients with long QT syndrome. *Br Heart J* 40: 1014, 1978.
4. Hugenholtz P G. Electrocardiographic abnormalities in cerebral disorders. Report of six cases and review of the literature. *Am Heart J* 63: 451, 1962.
5. Lepeschkin E. Physiologic basis of the U wave. In: *Advances in electrocardiography* (ed R C Schlant & J W Hurst) p 431. Grune & Stratton, New York, 1972.
6. Navarro-Lopez F, Cinca J, Sanz G, Periz A, Magrina J & Betru A. Isolated T wave alternans. *Am Heart J* 95: 369, 1978.
7. Ratshin R A, Hunt D, Russell R O Jr & Rackley C E. QT interval prolongation, paroxysmal ventricular arrhythmias and convulsive syncope. *Ann Intern Med* 75: 919, 1971.
8. Surawicz B. The pathogenesis and clinical significance of primary T wave abnormalities. In: *Advances in electrocardiography* (ed R C Schlant & J W Hurst) p 406. Grune & Stratton, New York, 1972.
9. Vincent G M, Abildskov J A & Burgess M J. Q-T interval syndromes. *Progr Cardiovasc Dis* 16: 523, 1974.



## Myasthenia Gravis and Werlhof's Disease

W A Veenhoven H J Oosterhuis and G S van der Schans

*From the Division of Hematology, Department of Medicine and the Department of Neurology, University of Groningen, Groningen, The Netherlands*

**TRACT** A case of Werlhof's disease (immune thrombocytopenia) associated with myasthenia gravis is described. The two disorders developed within a month of each other. The immunological and clinical aspects of the association are discussed.

**Keywords:** myasthenia gravis, thrombocytopenia, Werlhof's disease.

Acta Med Scand 206 131-1979

Werlhof's disease, thrombocytopenia has been reported to be due to accelerated destruction of platelets by an immune mechanism (9). Several types of the disease are recognized, e.g. idiopathic thrombocytopenia (ITP) when no exogenous factor is present and drug-induced or symptomatic thrombocytopenia in the course of certain other disorders (2). A humoral mechanism is considered responsible for platelet destruction. A cell-mediated mechanism has not been demonstrated convincingly.

Myasthenia gravis (MG) is a disorder of neuromuscular transmission which is probably due to an autoimmune attack reducing the available number of choline receptors of the postsynaptic membrane of skeletal muscle. This reduction has been demonstrated biochemically and histologically and is thought to have a direct relation with the circulating autoantibodies reacting with acetylcholine receptors (4). Immune complexes at the motor endplate (MEP) have been demonstrated (5). Thymic abnormalities are observed as thymomas in 10-15% of patients and follicular hyperplasia in 50-60% of patients with thymuses removed by operation. An authoritative review is given by Drachman (4). The association between MG and other autoimmune diseases has been reported frequently. Although epidemiologic studies are scarce, at least in rheumatoid arthritis (12) and thyroid disorders (16)

are more common in myasthenic women than can be expected. Pure red cell aplasia has some preference for myasthenic patients because of its association with a thymoma (11).

A number of associations of Werlhof's disease and other autoimmune disorders have been described. Immune thrombocytopenia may occur in the course of systemic lupus erythematosus (2) or in association with autoimmune hemolytic anemia (Evans' syndrome) (2). An association with Hashimoto's disease has been described (3). Three cases of MG associated with ITP have been reported recently (14, 15, 19). In these cases the disorders did not arise simultaneously. MG developed many years after the ITP (14, 19) or the reverse (15).

The present paper reports on a case of MG and Werlhof's disease occurring at about the same time.

## CASE REPORT

A 19-year-old man was in good health until Feb 1976 when he noticed a stiffness in his face and a strange way of laughing. In May 1976 swallowing and articulation became difficult and he experienced diplopia. Proximal weakness in arms and legs supervened. His symptoms increased after exercise and were more prominent at night.

The diagnosis of MG was made after a positive edrophonium chloride test and was confirmed by typical decremental response of the muscle action potentials after supramaximal stimulation of the nerve at a rate of 3 per second. Treatment with pyridostigmine bromide and pyridostigmine bromide was started in June and ambenonium chloride was added in August. Nevertheless his symptoms increased and he was brought to our hospital.

**Abbreviations:** ITP = idiopathic thrombocytopenia; MG = myasthenia gravis; MEP = motor endplate.

**Reprint requests to:** W A Veenhoven, Division of Hematology, Department of Medicine, University of Groningen, Oostersingel 59, Groningen, The Netherlands.

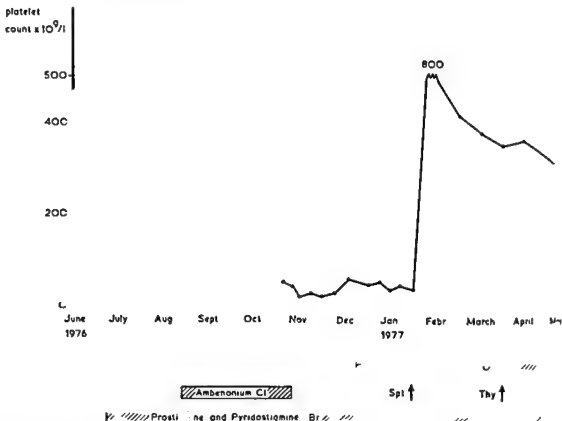


Fig 1 Clinical course P=prednisone (60=60 mg daily 60/0=60 mg on alternate days) Spl=splenectomy Thy=thymectomy

in Oct 1976 because of attacks of respiratory insuffi-

On admission he was in general good health with the typical picture of a generalized MG. His vital capacity at rest was reduced to 80% of the normal value. A chest X ray revealed no evidence of a thymoma and antimuscle antibodies were not detected. Thymectomy seemed indicated. Thrombocytopenia was detected at the routine laboratory examinations. There was no history of purpura or other bleeding manifestations. The family history was unremarkable and no bleeding disorders, myasthenia or thyroid diseases were known. The spleen was not palpable and no lymphadenopathy, goitre or bleeding manifestations were found.

The platelet count in an electronic particle counter confirmed by phase contrast microscopy ranged from 46 000 to 55 000/mm<sup>3</sup>. WBC was 7 800/mm<sup>3</sup> with a normal differential count. Serum electrophoresis and tests for renal hepatic functions revealed normal findings. Cultures of urine and sputum were negative.

Examination of a bone marrow smear revealed an increased number of megakaryocytes with a normal appearance. Survival of <sup>51</sup>chromium labelled donor platelets was markedly shortened to 72 hours. Coagulation tests yielded normal results. Serum thyroxine level was within the normal range 8.7 µg/100 ml. Tests for rheumatoid factor

antinuclear and antithyroid antibodies gave negative results. The patient's blood group was B Rhesus +. HLA typing A<sub>1</sub> A<sub>2</sub> B<sub>3</sub> B<sub>1</sub>. Cytotoxic cross antibodies were not found. The complement C<sub>3</sub> normal.

The diagnosis of Werlhof's disease (thrombocytopenia) was made. None of the drugs the patient have been reported to provoke a thrombocytopenia.

Ambenonium chloride—the only drug that had been added recently—was withheld. In the next 6 weeks the platelet count did not increase and ranged from 40 000/mm<sup>3</sup>. Subsequently treatment with prednisone in a dose increasing from 30 to 60 mg daily was started. In the next six weeks the platelet count rose somewhat but did not exceed 65 000/mm<sup>3</sup>. The bleeding time was 7–9 min. The myasthenia improved only partially. Prednisone treatment was continued on an alternate dose scheme. Splenectomy was considered. Thymectomy was contraindicated by the persistent thrombocytopenia.

Splenectomy was performed in Jan 1977. It was followed by a prompt and sustained remission of the thrombocytopenia. The platelet count remained above 300 000/mm<sup>3</sup>. Thymectomy was performed two months later. Following both operations a short period of ventilatory assistance was

## I Immunological data on the patient

of disease	Thrombocytopenia	Remission of thrombocytopenia	
		1 week	6 months
gent	Untreated	Prednisone splenectomy	Thymectomy
Platelet antibodies	-	-	-
Antibodies to platelets	+	-	+
Antibodies to bound IgM	Weak	-	-
Antibodies to bound IgG	++	+	-
Antibodies to skeletal muscle	-	-	+
	(1/10)		(1/4)
Antibodies to MEP	Dubious		+
			(1/10)

Histological examination of the spleen revealed no abnormalities. A few germinal follicles were found in the spleen and there was no thymoma. Following the treatment the myasthenic symptoms decreased and prednisone dosage could be reduced gradually but could not be discontinued. The clinical course is summarized in Fig. 1. A recent respiratory tract infection was followed by a short exacerbation of the myasthenia. Thrombocytopenia remained in remission.

Immunological studies were performed on several occasions during the course of the disease.

Antibodies to skeletal muscle were detected by an indirect immunofluorescence technique described by Felt et al. (7). Only fluorescent anti IgG sera were used. Antibodies to MEP were detected by an indirect immunofluorescence technique using fluorescent anti IgG sera recently described by Sontag-Tschroots et al. (8).

Antibodies to bound immunoglobulins were detected by direct immunofluorescence on gel filtered platelets as previously described (17).

Platelet antibodies were detected in sera by an indirect immunofluorescence technique previously described (18). Serum and platelet rich plasma prepared from anticoagulated blood were incubated, washed by centrifugation and stained with fluorescent rabbit antihuman IgM.

Results of the immunological studies are given in Table I.

In a control study no platelet antibodies were found in sera of 12 patients with active MG and no skeletal muscle antibodies were detected in the sera of 12 patients with Werlhof's disease.

## DISCUSSION

The association of MG and ITP has been reported in a few cases in the past two years. Segal and Traub (19) described a patient with ITP who was in remission after splenectomy and developed

Hashimoto's disease and MG ten years later. Pinals et al. (14) described a patient with Graves' disease followed by ITP and 12 years later by MG. Remuzzi et al. (15) described a patient with MG who developed ITP ten years later. All these patients were females. Platelet antibodies were found in the first case by a platelet factor 3 release assay and in the last case by a serotonin release test. The antibodies were not characterized. HLA typing did not show a definite association between HLA type and disease. HLA B<sub>1</sub> was found in the former two cases and HLA B<sub>8</sub> in the latter case.

MG has a prevalence of 2.4 and 8.6 per 100,000 respectively for men and women (10). The prevalence of Werlhof's disease is not exactly known but is estimated from clinical admission data to be about 4 per 100,000. The female:male ratio in Werlhof's disease is about 3:1. Thus the chance of coincidence of MG and Werlhof's disease is extremely small, especially with respect to males. In a series of 400 consecutive patients with MG observed by one of us (H.J.O.) only one patient was seen who probably had suffered from Werlhof's disease in the past: a young woman suffering from MG from the age of 27 who underwent splenectomy at the age of 22.

Our present patient is a young man who developed MG and ITP within a few months of each other. The thrombocytopenia was discovered on a routine examination after intake of anticholinergic drugs for several months. Withdrawal of ambenonium chloride did not change the platelet count notably; the other drugs could not be withheld without endangering the patient but they are not known to have elicited an immune



**thrombocytopenia** Remission of the ITP was not achieved on prednisone treatment but splenectomy was followed by a persistently normal platelet count

On admission IgG platelet antibodies were found in the patient's serum and IgG as well as small quantities of IgM on his platelets. The serum antibodies persisted throughout the course but the platelet IgM disappeared in a few weeks, the IgG several weeks later when remission was reached. The rapidly disappearing IgM is consistent with the recent onset of immune thrombocytopenia. After splenectomy IgG antibodies were still present in the serum. Because a platelet transfusion had been given for survival studies, the presence of isoantibodies at that time cannot be ruled out. Platelet bound antibodies were not detected six months after splenectomy.

IgG antibodies to skeletal muscle were not found initially when a 1:10 diluted serum was tested. They were detected however when a dilution of 1:4 was used. Thus they were found in a very low titer. IgG antibodies to MEP were detected most clearly in a later phase of the disease when thymectomy had been performed and the patient was still on prednisone. IgG antibodies to skeletal muscle are found in 22% (7) and antibodies to acetylcholine receptor substance in 87% (4) of MG cases.

Serum platelet antibodies belonging to the IgG  
s are found in about 60-70% of patients with

P (9) Platelet antibodies were not found in the sera of our 12 control patients with MG and skeletal muscle antibodies were not detected in 12 control patients with Werlhof's disease. Platelet antibodies are supposed to be produced largely in the spleen but also in other parts of the reticuloendothelial system (9). Production of acetylcholine receptor antibodies by thymic lymphocytes has been reported recently (22). In our patient antibodies to MEP were however still present after thymectomy. Whether the platelet and MEP IgG antibodies are cross reacting or independent cannot be determined from our data.

A modest association between MG and HLA B<sub>8</sub> has been described by several authors (7). Goebel et al (8) reported an association between ITP and HLA B<sub>8</sub> and HLA B<sub>12</sub>. In a recent study we could however not find associations of any significance (21). Neither B<sub>8</sub> nor B<sub>12</sub> are present in the patient presented here.

The practical consequence of the association of autoimmune disorders is to carefully search for others when one of them has been found. This is especially important when an operation such as splenectomy, thymectomy or thyroidectomy is considered. Serious complications—such as bleeding due to thrombocytopenia, respiratory insufficiency, or in myasthenia or thyrotoxic crises—may be prevented by adequate preoperative treatment.

## REFERENCES

- 1 Bach F H & van Rood J J Tc histocompatibility complex N Engl J Med 1976
- 2 Baldini M Idiopathic thrombocytopenic purpura N Engl J Med 271 1245 1301 1360 1966
- 3 Crabtree G R Lee J C & Cornwell G C Immune thrombocytopenic purpura and myasthenia gravis. Ann Intern Med 83 371 1975
- 4 Drachman D B Myasthenia gravis N Engl J Med 298 136 186 1978
- 5 Engel A G Lambert E H & Howard F Immune complexes (IgG and C<sub>3</sub>) at the motor endplate in myasthenia gravis Mayo Clin Proc 1977
- 6 Engel A G Lindstrom J M Lambert E H & Lennon V A Ultrastructural localization of acetylcholine receptor in myasthenia gravis: an experimental autoimmune model Neurology 1977
- 7 Felikamp T E W van den Berg Loonen H J Nijenhuis L E Engelfriet C P van Rood C L van Loghem J J & Oosterhuis H J Myasthenia gravis autoantibodies and HLA Br Med J 1 131 1974
- 8 Goebel K M Hahn E & Havemann H Matching in autoimmune thrombocytopenic purpura Br J Haematol 35 341 1977
- 9 McMillan R The pathogenesis of thrombocytopenic purpura CRC Crit Rev Clin Lab Sci 8 303 1977
- 10 Oosterhuis H J G H Epidemiology of Myasthenia in Amsterdam In Myasthenia Gravis (Hertel u A) pp 103-108 Thieme Stuttgart 1977
- 11 Oosterhuis H J G H Felikamp T E W Rossum A L van den Berg Loonen D M Nijenhuis L E HLA antigens auto-antibodies and associated diseases in patients with myasthenia gravis and with and without myasthenia gravis Acad Sci 274 468 1976
- 12 Oosterhuis H J G H & De Haas W F Rheumatic diseases in patients with myasthenia gravis Acta Neurol Scand 44 219 1968
- 13 Oosterhuis H J G H Sluiter A H C Felikamp T E W & van der Geld H Myasthenia gravis combined with thymoma and aplastic anaemia Tijdschr Geneesk 109 308 1964
- 14 Pinals R S Russell H T Haas D C & Fox

s disease myasthenia gravis and purpura *Ann Med* 87 250 1977

zzi G Livio M Donati M B & de Gaetano *Myasthenia gravis thrombocytopenia and HLA* *Ann Intern Med* 87 250 1977

arbullo J *Myasthenia gravis and hyperdisin in neurology* *Proceedings X Int Congress Neurology Excerpta Medica Congress Series* 319 975

er Schans G S Veenhoven W A Metting *Platelet membrane associated immunoglobulins complement in some blood disorders by direct* *Immunofluorescence (abstr)* *Br J Haematol* 35 679 1977

er Schans G S Veenhoven W A Snijder J & Nieweg H O *The detection of platelet*

*iso-antibodies by membrane fluorescence* *J Clin Lab Med* 90 4 1977

19 Segal B M & Weintraub M I Hashimoto's *thyroiditis myasthenia gravis idiopathic thrombocytopenic purpura* *Ann Intern Med* 85 761 1976

20 Sontag Tschroots I R J M Schulz Raateland R C M van Walbeek H K & Felikamp T E W *Antibodies to motor endplates demonstrated with the immunofluorescence technique* *Clin Exp Immunol* In press 1979

21 Veenhoven W A Kaars Sijpesteijn J A & van der Schans G S *HLA antigens in idiopathic thrombocytopenic purpura* *Acta Haematol* In press 1979

22 Vincent A Thomas H C Scadding G K & Newsom Davis J *In vitro synthesis of anti acetylcholine receptor antibody by thymic lymphocytes in myasthenia gravis* *Lancet* i 305 1978



# Effects on Muscle Electrolytes of Potassium and Magnesium Infusions, Spironolactone Medication and Operation in a Case of Primary Aldosteronism

Thomas Dyckner and P O Wester

*From the Departments of Medicine Serafimerlasarettet Stockholm and University Hospital Umeå Sweden*

**R**ACT Serum and muscle electrolytes were used in a case of primary aldosteronism before and after potassium and magnesium infusions as well as spironolactone treatment and following surgery. Potassium infusions resulted in a transient increase of the muscle potassium (K/m) for within 3-4 days by a return to the previously low level. Magnesium infusions did not give any increase in muscle magnesium (Mg/m). On the contrary there was a decrease in Mg/m concomitant with a decrease in K/m. Treatment with spironolactone for one month was followed by a normalization of both serum and muscle electrolytes. After surgery the serum potassium and K/m returned to normal, but the serum magnesium (Mg/s) and Mg/m showed a decrease to subnormal values. The initial findings of normal Mg/s and Mg/m as excretion of more than 80% of the daily sodium dose thus may indicate that there was a sodium deficiency in the skeletal pool.

magnesium in a case of primary hyperaldosteronism before and after potassium and magnesium infusions. We have also studied the effects of treatment with an aldosterone antagonist spironolactone (Aldactone<sup>®</sup>) on the muscle electrolytes.

## METHODS

Muscle biopsies were obtained *ad modum* Bergstrom (2) from the lateral portion of the quadriceps femoris muscle after an overnight fast. The biopsies (40-80 mg wet weight) were weighed repeatedly on an electrobalance after carefully dissecting them free from visible connective tissue and fat. The wet weight was obtained by extrapolation to zero time. The dry weight was obtained after drying to constant weight in an oven. Fat was extracted with redistilled petroleum ether. The muscle pieces were wet ashed in 1N nitric acid and the contents of sodium, potassium and magnesium were determined by atomic absorption spectrophotometry. Chloride was determined indirectly after precipitation with silver nitrate. The silver residues were determined by atomic absorption spectrophotometry. The intracellular electrolytes were calculated according to the chloride method (12) assuming chloride is freely diffusible across the cell membrane. A normal resting membrane potential (4) was used to calculate the chloride equilibrium over the cell membrane. The serum and muscle electrolytes are presented in Table I.

## CASE REPORT AND RESULTS

The patient was a 55-year-old woman who had difficulties in concentrating and was investigated at a psychiatric clinic in 1967. Arterial hypertension was found and the patient was treated with various diuretics and later with  $\beta$ -blocking agents without success. She had a tendency to a low serum potassium level despite a high potassium supplementation. She often had headaches in the occipital region, mostly in the morning. During the last two years

**Abbreviations** m=muscle s=serum ec=extracellular ic=intracellular

Table 1 Serum and muscle electrolytes

FFDS = fat free dry solid

Biopsy no	Serum (mmol/l)		Muscle (g/100 g FFDS)			Muscle (mmol/100 g FFDS)		
	K	Mg	H <sub>2</sub> O/m	H <sub>2</sub> O/ec	H <sub>2</sub> O/ic	Cl/m	Na/m	K/m
I	2.2	0.78	385	72.4	313	9.06	23.4	38.2
II	3.0	0.81	363	85.8	277	10.8	17.5	40.6
III	2.8	1.29	447	219	229	26.3	32.8	34.0
IV	3.9	0.80	378	80.2	298	10.8	14.5	44.8
V	3.5	1.07	379	167	212	20.2	25.1	33.3
VI	4.2	0.90	381	105	276	14.0	19.4	45.4
VII	4.6	0.67	423	138	285	19.5	19.6	44.7
Normal values	3.6-5.4	0.80-1.00	305-384	<120	231-315	<14.0	<19.0	40.8-48.4

she also complained of vertigo and chest pains on heavy exertion. She had also observed a successively increasing muscular weakness.

In 1976 she visited the emergency ward because of a painful shoulder. A blood pressure of 260/125 mmHg was registered. On admission she had a very low serum potassium (K/s) (2.2 mmol/l), normal serum sodium (Na/s) (141 mmol/l), slightly low serum magnesium (Mg/s) (0.78 mmol/l) and a high total carbonate (31 mmol/l). A renal X-ray showed no abnormalities. The urinary excretion of aldosterone was clearly above normal and the renin values were extremely low.

A muscle biopsy (I) was performed on admission and showed a low muscle potassium (K/m) content and a high muscle sodium (Na/m) content. The muscle magnesium content (Mg/m) was normal. The intracellular concentration of sodium (Na/ic) was high and that of potassium (K/ic) very low. The patient was given 500 mmol potassium chloride by vein, but the K/s was still below normal (3.0 mmol/l). A second muscle biopsy (II) showed that K/m had increased to nearly normal and K/ic to normal and Na/m had decreased.

Two days later, after infusion of 30 mmol magnesium sulphate and only oral potassium supplementation, a third muscle biopsy (III) was performed. The analyses showed a rapid retreat to the original low K/m and high Na/m values. Mg/m, however, decreased. In the interval between biopsies II and III the patient had excreted more than 300 mmol potassium in urine.

She was again given i.v. potassium supplementation this time till a normal K/s was obtained. A new muscle biopsy (IV) again showed that the K/m values increased this time to normal values for both K/m and K/ic. Four days afterwards, following an infusion of 30 mmol magnesium sulphate and only oral potassium supplementation, a new muscle biopsy (V) showed a repetition of the retreat to pretreatment values and a decrease in Mg/m. During these four days she had excreted about 1000 mmol potassium in urine. In the 24 hours following the magnesium infusion, 26 mmol magnesium was excreted in the urine.

Thereafter the patient was treated with spironolactone (Aldactone®) 25 mg×4 by mouth for one month. The serum electrolyte values following this treatment showed

a normalization of all electrolytes including total carbonate and K/m increased to normal values for K/s and K/ic (VI). Two months later the patient was upon and a cortical glomerulosa adenoma of C was excised.

Two months after the operation, during which the patient was off medication, a last muscle biopsy was performed (VII). All serum electrolyte values were normal and about the same as after spironolactone treatment, except for magnesium, which had decreased to normal levels. K/m and Na/m had also normalized. Mg/m had decreased.

## DISCUSSION

Our studies confirm the earlier findings of low K/m and K/ic and increased Na/m and primary hyperaldosteronism (5-8, 15). The K/m was normal, which speaks against a muscular potassium deficiency. It is quite obvious in our case that administration of large amounts of i.v. potassium resulted in a rapid excretion through the kidneys. The potassium supplementation gave only a transient increase in K/s for one or two days.

Spironolactone is a well known and powerful inhibitor of aldosterone and has been shown to normalize the K/s level in cases with excessive aldosterone production (9). This proved to be the case in our patient who showed a return to normal K/s and Mg/m. Thus spironolactone seems to be effective in the treatment of hyperaldosteronism and its associated diseases, nephrosis and congestive heart failure, which may be further accentuated by the use of thiazides and furosemide (10, 14); this may require more liberal use of spironolactone in the treatment of these diseases.

	mEq/kg H <sub>2</sub> O/ic	
	K/ic	Mg/ic
1	122	14.3
2	146	15.2
3	146	16.8
4	149	13.4
5	154	14.4
6	163	14.5
7	153	12.9
8	143-191	12.4-17.8

potassium infusion, both K/m and K/ic in  
This was confirmed in a repeated trial  
is points to a normal Mg/m content as it is  
wn that magnesium stimulates the Na K  
- which is needed to promote the ingress of  
- into the cell

- magnesium infusion the urinary potassium  
7 was high and K/m decreased greatly as  
potassium was administered Mg/m  
a paradoxical decrease. The same hap-  
after a repeated magnesium infusion. A  
relation between K/m and Mg/m has been  
rated earlier (1) and may perhaps help to  
he paradoxical decrease in Mg/m. Another  
on may be the primary aldosteronism per  
s been shown (3) that when potassium is  
in this disease there may be an increase in  
ne secretion and an increased loss of  
in the urine. Concomitantly there may  
an increased urinary loss of magnesium  
/m decreases the intracellular water de-  
in parallel. Thus the cell seems to try to  
c constant

magnesium infusion 90% of the infused Mg  
reted in the urine during the first 24 hours  
en found (16) that an excretion of less than  
icates magnesium deficiency while more  
% contradicts deficiency. Again the finding  
atient of an excretion of 90% of the given  
is in favour of a normal body magnesium

lood pressure returned to normal after op-  
without any further medication. The extra-  
acellular electrolytes normalized except for  
d Mg/m which both showed low values  
th urinary magnesium excretion as de-

scribed in primary aldosteronism (11) together with  
a normal Mg/m may be explained if Mg is lost from  
the skeleton during aldosterone hypersecretion.  
In that case the skeleton should try to attract  
magnesium after operation to compensate for the  
earlier losses. The low values of Mg/s and Mg/m  
found in our patient after operation are in ac-  
cordance with such a theory.

### ACKNOWLEDGEMENT

Financial support was given by the Swedish National As-  
sociation against Heart and Chest Diseases.

### REFERENCES

- Baldwin D, Robinson P K, Zierler K L & Lil-  
ienthal J L Jr. Interrelations of magnesium, potas-  
sium, phosphorus and creatine in skeletal muscle of  
man. *J Clin Invest* 31: 850, 1952.
- Bergstrom J. Muscle electrolytes in man determined  
by neutron activation analysis on needle biopsy  
specimens. A study on normal subjects, kidney pa-  
tients and patients with chronic diarrhoea. *Scand J  
Clin Lab Invest (Suppl)* 68: 1, 1962.
- Biglieri E G & Forsham P H. Studies on the  
expanded extracellular fluid and the responses to var-  
ious stimuli to primary aldosteronism. *Am J Med*  
30: 564, 1961.
- Bolte H D, Riecker G & Rohl D. Messungen  
des Membranpotentials an einzelnen quergestreiften  
Muskelzellen der Menschen in situ. *Klin Wochenschr*  
41: 356, 1963.
- Van Buchem F S P. The electrocardiogram and  
potassium metabolism. Electrocardiographic abnor-  
malities in primary aldosteronism and familial pe-  
riodic paralysis. *Am J Med* 23: 376, 1957.
- Bucht H, Bergstrom J, Lindholmer N, Wynblad H  
& Hokfelt B. Catheterization of the left adrenal  
vein for contrast injection and steroid analysis in a  
case of Conn's syndrome. *Acta Med Scand* 176: 233,  
1964.
- Chalmers T M, Fitzgerald M G, James A H  
& Scarborough J. Conn's syndrome with severe  
hypertension. *Lancet* i: 127, 1956.
- Conn J W. Primary aldosteronism: a new clinical  
syndrome. *J Lab Clin Med* 45: 3, 1955.
- Conn J W, Louis L H, Fajans S S, Streeten D,  
H P, Johnson R H, Moorhouse J R, Crane M,  
G, Berker A F & Ramirez E. Metabolic effects in  
normal men and in primary aldosteronism of a syn-  
thetic aldosterone antagonist. *J Lab Clin Med* 52: 805,  
1958.
- Crabbé J, Ross E J & Thorn G W. The signifi-  
cance of the secretion of aldosterone during dietary  
sodium deprivation in normal subjects. *J Clin En-  
doocrinol Metab* 18: 1159, 1958.
- Dupasquier E. Un cas de syndrome de Conn asym-  
ptomatique. *Schweiz Med Wochenschr* 95: 226, 1965.

- 12 Graham J A, Lamb J F & Linton A L. Measurements of body water and intracellular electrolytes by means of muscle biopsy. *Lancet* 2: 1172, 1967.
- 13 Hanna S & MacIntyre I. The influence of aldosterone on magnesium metabolism. *Lancet* 2: 348, 1960.
- 14 Laragh J H, Sealey J E & Sommers S C. Patterns of adrenal secretion and urinary excretion of aldosterone and plasma renin activity in hypertensive subjects. *Circ Res* 18: 144, 1966.
- 15 Milne M D, Muehrcke R C & A-2.1. Aldosteronism. *Proc R Soc Med* 49: 831, 1956.
- 16 Thorén L. Magnesium deficiency in the rat: fluid loss. *Acta Chir Scand (Suppl)* 394: 1-12, 1965.

# The Syndrome of Inappropriate Secretion of Antidiuretic Hormone

## A Case Report

Erk Hagg Folke Lithner Bengt Lindqvist and Frej Fyhrquist

*From the Department of Internal Medicine University Hospital Umeå Sweden  
and the Minerva Institute for Medical Research Helsinki Finland*

**ACT** A 72 year-old woman with the syndrome of inappropriate secretion of antidiuretic hormone of unknown cause during more than one observation is reported. Plasma vasopressin was excessively elevated, even during a water load. Her serum electrolyte abnormalities and state were ameliorated after fluid restriction. Treatment with demeclocycline the patient to increase fluid intake without deteriora-

tion. She has never had any skull trauma or meningoencephalitis. On July 7 1977 she fell acutely ill with fever (about 38-39°C) malaise frequent urination and mental confusion.

On admission to the local hospital five days later she was still confused. No edema or signs of dehydration were noted. Temperature was 39.3°C and BP 150/80 mmHg. There were no pareses. The tendon reflexes were difficult to elicit but without asymmetry. There was a mild neck rigidity but Lasègue's sign was negative. ESR blood Hb level leukocyte count serum bilirubin GOT and GPT levels were normal. On the day of admission serum sodium was 115 mmol/l chloride 79 mmol/l and creatinine 70 µmol/l. Serum potassium was initially 3.8 mmol/l but tended later to be low (minimum value 2.2 mmol/l) as did serum calcium (minimum value 1.8 mmol/l). Repeated blood cultures were negative. A urinary culture showed significant bacteriuria the sediment containing increased amounts of erythrocytes and leukocytes. A diagnosis of acute cystopyelitis was made and the patient received antibiotics. The fever decreased after one week a low grade fever persisting for another two months.

Because of the severe serum electrolyte abnormalities the patient was also treated with sodium chloride 3-7.5 g daily together with glucocorticoids and fluorhydrocortisone. Serum sodium and chloride increased but remained subnormal serum sodium levels were most of the time below 130 mmol/l and chloride below 90 mmol/l. Potassium chloride and calcium gluconate lactate were also administered. Daily urinary output varied between 1 and 3.8 l. Urinary excretion of sodium was 171-444 mmol/24 h and of potassium 26-167 mmol/24 h.

After four weeks in the local hospital she was referred to the Department of Internal Medicine Umeå University Hospital where she was treated on four occasions during the period Aug 1977-Oct 1978.

On the first admission the patient was bed ridden and disorientated. There was a generalized muscular wasting but the results of the neurological examination were normal. Eye ground examination revealed no papilledema. ECG showed a sinus tachycardia and Q waves in I aVL and V<sub>4-7</sub>. A bronchoscopy was normal as were repeated

*Is vasopressin hyponatremia demeclocycline*  
*J Scand 206 141 1979*

syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is characterized by water retention hyponatremia low serum osmolality essence of urinary osmolality which is less osmotically dilute and continued renal excretion of water (1). The syndrome has been described in connection with a variety of diseases, the most frequent being malignancy (most often lung carcinoma) disorders of the central nervous system and primary diseases (2). In addition certain drugs such as chlorpropamide and carbamazepine can cause SIADH (4).

We describe a woman who presented the features of SIADH but in whom we have hitherto been unable to reveal an underlying cause. Measurement of plasma ADH after a water load showed high levels. In addition the result of short treatment with demeclocycline is reported.

## CASE REPORT

The patient was a 72 year-old woman who since 1958 has had allergic rhinitis and bronchial asthma. She has been treated with modulators and expectorants and since 1960 with diazepam (triamcinolone) 4 mg daily. For as long as she can remember she has had a tendency to thirst with

**Abbreviations** ADH = antidiuretic hormone SIADH = syndrome of inappropriate secretion of ADH



Table 1 Result of water loading test

Time (h)	Serum osmolality (mosmol/kg)	Urine osmolality (mosmol/kg)	Serum sodium (mmol/l)	Plasma vasopressin (pg/ml)
0	245	412	129	39.6
08	255	481	127	36.3
10	265		129	31.7
12	270	481	127	64.5
14		750 ml of water ingested		
14-30	260			42.9
16	265	304	124	44.6
18	275	233	124	56.1

chest X rays (the last one performed in Oct. 1978) and an i.v. pyelography. Renal arteriography did not reveal any abnormalities of the kidneys. A liver scan was normal. X ray examination of the pituitary fossa and EMI scanning of the brain were normal except for a moderate bilateral widening of fissura Sylvii. Echoencephalography showed a slightly increased width of the third ventricle. EEG—initially pathological with a pronounced episodic bilateral synchronous abnormality probably projected from subcortical structures—was quite normal in April 1978. EMG of the upper and lower limbs was normal. Repeated lumbar punctures (Aug. 29, Sept. 7 and 27, Oct. 28, Dec. 8, 1977 and Jan. 4, 1978) were normal except for an elevated protein content which eventually decreased to normality: 1010, 1090, 765, 525, 511, 398 mg/l. Spinal fluid electrophoresis initially showed a slight oligoclonal increase of IgG which later disappeared. Blood WR was negative. Serum and urinary electrolyte values were unchanged. Urinary concentration ability during thirst was 775 mosmol/kg and did not increase after intranasal administration of 20 µg of the synthetic vasopressin analogue desmopressin (Mininn®). There was no glucosuria. Urinary porphobilinogen was normal.

When suspicions of SIADH were raised, glucocorticoids and fluorhydrocortisone were omitted and the daily fluid intake was reduced to 0.5–1 l. In four days serum sodium levels had increased from about 120 to 130 mmol/l and serum chloride levels from about 90 to 97 mmol/l and thereafter most of the serum values for sodium were 130–135 and for chloride 94–104 mmol/l. In addition serum potassium and calcium rose to normal levels. A few days after fluid restriction had been initiated the patient's mental condition improved and she could sit in a chair. After three weeks her mental state was entirely restored and she began to walk.

#### Water load test and plasma ADH measurements

A water load test was performed on Oct. 12, 1977. During the test no food or fluid was given after midnight. At 2 p.m. the patient ingested 750 ml of water during 15 min. Specimens were taken for plasma ADH, serum and urine osmolality and serum sodium assays. Plasma ADH was measured with radioimmunoassay (3). The results are shown in Table 1. It will be seen that serum osmolality (measured by the freezing point method) was low, ranging from 245 to 275 mosmol/kg H<sub>2</sub>O. Plasma ADH showed

excessively elevated levels (normal value <4 mosmol/kg H<sub>2</sub>O of serum osmolality) with a rise during thirst and a decrease after fluid administration.

#### Other endocrine investigations

Serum FSH, prolactin, TSH, thyroxine and were normal (the latter showing an overt rhythm). During an insulin hypoglycemia test cortisol values rose from 542 to 853 nmol/l. Serum LH concentration was somewhat low (normal value 18–125 arb. U/l). A TRH test. Urinary excretion of aldosterone was normal.

#### Demeclocycline trial

Demeclocycline (Ledermycin®) 900 mg daily orally for 8 days. Fluid intake was increased from about one to two l/24 h. A body weight was unaltered and serum sodium significantly during the treatment period. I did not complain of any subjective symptoms. The demeclocycline was discontinued, her daily fluid intake reduced to about one liter as before.

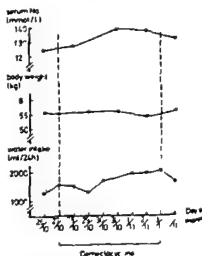


Fig. 1 Response to demeclocycline (Ledermycin®) 900 mg daily.

# DISCUSSION

patient fulfills the criteria of SIADH as summarized by Bartter and Schwartz (1): 1) hyponatremia with corresponding hypo-osmolality of the plasma; 2) continued renal excretion of sodium; 3) absence of clinical evidence of fluid volume depletion; 4) normal skin turgor and BP; 5) osmolality of urine higher than that appropriate for the osmolality of the plasma; 6) normal renal function; 7) normal adrenal function. An additional feature of SIADH is that the signs of the syndrome are reversed by fluid restriction.

The cardinal features of SIADH can be reversed by administration of vasopressin and water. In SIADH patients, measurement of ADH in plasma and urine after a water load has shown decreased levels of the hormone, confirming that the excretion is inappropriate relative to plasma osmolality (4). Our patient had very high plasma ADH levels even after a water load.

The cause of the inappropriate secretion of ADH in our patient is unknown. We have not been able to find any pulmonary or malignant disease during her one year's observation. Furthermore, she has not received any drugs reported to induce SIADH (4). There are several reports on SIADH in association with different kinds of intracranial lesions (5). When the acute phase of the disorder has passed, the SIADH also promptly disappears (1). Our patient had an increase of spinal fluid protein, indicating some disease of the CNS. She had never had encephalitis, but the persistence of elevated ADH speaks to some extent against this diagnosis. It seems likely that the patient has a CNS disorder resulting in inappropriately high levels of ADH. This hypersecretion of ADH appears to be only partly controlled by fluid intake

(Table 1): serum osmolality or serum sodium concentration. Thus, a simple resetting of the osmostat for ADH release (4) could not be demonstrated. The ADH hypersecretion displayed a rather autonomous pattern.

The patient has a long history of polydipsia, presumably of the primary psychogenic type. Hyponatremia occurs in rare cases of primary polydipsia (1). However, in these instances, urine is nearly maximally dilute and plasma ADH levels are suppressed, in contrast to the findings in our patient. The history of polydipsia may indicate that both the thirst regulating and the ADH regulating centres of the CNS were damaged in our patient.

Demeclocycline blocks the antidiuretic action of vasopressin in the renal collecting duct and has therefore been administered to patients with SIADH (2). During a short term therapeutic trial with this drug, our patient was able to increase her daily fluid intake from one to two liters without untoward effects. This effect of the ADH antagonizing drug, demeclocycline, further supports the view that the dilution syndrome observed in our patient was indeed due to inappropriate hypersecretion of ADH.

# REFERENCES

1. Bartter F C & Schwartz W B. The syndrome of inappropriate secretion of antidiuretic hormone. *Am J Med* 42: 790, 1967.
2. Forrest J N, Cox M, Hong C, Morrison G, Blaustein M & Singer I. Superiority of demeclocycline over lithium in the treatment of chronic syndrome of inappropriate secretion of antidiuretic hormone. *N Engl J Med* 298: 173, 1978.
3. Fyhrquist F, Wallenius M & Hollemans H J G. Radioimmunoassay of vasopressin in unextracted plasma. *Scand J Clin Lab Invest* 36: 841, 1976.
4. Moses A M, Miller M & Streeten D H P. Pathophysiologic and pharmacologic alterations in the release and action of ADH. *Metabolism* 25: 697, 1976.

## ANNOUNCEMENTS

*The Basel Liver Week* will be held at the Mustermesse Basel Switzerland Oct. 3-8 1979 with Dr H. Popper New York, as Honorary President. The Liver Week will be centered by the V International Liver Conference which will be presided by Professor D. S. Sherlock.

*Further information:* Prof. Dr L. Bianchi, Dept. of Pathology, University of Basel, Schönheimstrasse 40, CH-4003 Basel, Switzerland.

*The VI Asia Pacific Congress on Diseases of the Chest* dealing with the medical and surgical aspects of lung diseases and sponsored by the International Society of Chest Physicians and Surgeons (Asian Pacific College of Chest Physicians) will be held in Bombay, India, Nov. 18-22 1979.

*Further information:* Dr A. R. Bhowmik, General VI Asia Pacific Congress on Diseases of the Chest, L. D. Ruparel Medical Centre, Dr Ambedkar Road, Worli, Bombay 40025, India.

# Coronary Arteriography in 486 Patients— Arteriographic Pathology and Prognosis

Staffan Ljungberg<sup>1</sup> Sven Åke Forsberg<sup>2</sup> Sven Paul n<sup>3</sup>  
and Lars Werko<sup>4</sup>

From Department 1 of Internal Medicine and Department 1 of Radiology, Sahlgrenska Hospital, University of Göteborg, Göteborg, Sweden

**ACT** The coronary arteriographic findings in a series of 486 non surgically treated patients were analyzed. A semiselective injection was made and the number and causes of deaths were from the census registry after a follow up of 7–12 years. The material comprised normal arteries in 26% of the patients, wall irregularities at most in 17%, obstruction of at least 50% diameter in 37% and unclassifiable arteries in 19%. A mean of 1.8 obstructed arteries per patient was found in the group with severe arterial lesions and among these patients anterior descending artery was most often

In the same group the cardiac mortality at 7 years was 20%. There were no significant differences between deceased and survivors with regard to arterial data. The arteriograms themselves offered information about the prognosis. Normal or wall irregularities at most implied excellent prognosis with regard to death in coronary heart disease. The seven year mortality was 36% among patients with coronary artery occlusions, which is notably higher than 14% among those with stenosis. Materials from the USA and Canada displayed a much higher mortality than ours in spite of comparable arteriographic findings.

*ds* coronary disease/mortality coronary vessel angiography

Acta Med Scand 206 145 1979

on the long term medical course of patients referred to coronary arteriography before the institution of coronary surgery provide an opportunity to investigate the natural history of coronary heart disease. The results of such studies may establish a baseline prognosis from which to judge the effect of coronary surgery and other new therapies. The present report contains an analysis of the

arteriographic findings in 486 patients. It also describes the extent and severity of the arterial lesions as seen in the arteriographs and their prognostic significance for mortality.

## PATIENTS

The study was based on all 510 coronary arteriographies carried out at Sahlgrenska Hospital between the beginning of 1961 and the middle of 1966. Of these 18 were re-arteriographies and were therefore excluded. Four patients who had emigrated and two who had undergone coronary surgery during the period of clinical follow up were also excluded from further analysis, which thus comprised 486 patients.

The indications for coronary arteriography were primarily to verify the existence and degree of coronary artery disease or coronary heart disease. In 227 patients (47%) the clinical findings often including chest pain suggested coronary heart disease as one of several diagnostic possibilities. In 148 patients (30%) coronary heart disease was considered to be present. Coronary arteriography was performed in these patients to assess the severity and extent of arterial pathology. The remaining 111 patients (23%) comprised cooperative investigation of valvular and congenital heart lesions or diagnostic studies in patients with hypertension, asymptomatic hyperlipidemia, cardiac enlargement of unknown cause, ECG abnormalities and idiopathic atrial fibrillation.

*Present addresses:* Med. Clin. C. Alingsås Hospital S-441 01 Alingsås, Sweden. <sup>2</sup> Med. Clin. C. Borås Hospital S-501 15 Borås, Sweden. <sup>3</sup> Department of Radiology, Beth Israel Hospital, 330 Brookline Avenue, Boston, MA 02215, USA. <sup>4</sup> Astra Lakemedel AB, S-151 85 Sodertälje, Sweden.

*Addess for reprints:* S. Ljungberg, Med. Clin. C. Alingsås Hospital S-441 01 Alingsås, Sweden.

*Abbreviations:* R, right coronary artery; M, main stem of the left coronary artery; LAD, left anterior descending coronary artery; LCA, left circumflex coronary artery.

Table I Comparison between distribution of obstructions in 179 of our patients and in 588 patients published by Proudfit et al (17)

	Our series		Proudfit et al (%)
	N	%	
<i>No. of arteries obstructed</i>			
One	86	48	34
Two	50	28	37
Three	36	20	26
Four	7	4	3
<i>Coronary arteries</i>			
Left M only	5	3	0.5
Left M with			
LAD	2	1	0.7
LCA	0	0	0.5
R	0	0	1.7
LAD and LCA	2	1	0.9
LAD and R	4	2	2.2
LCA and R	2	1	0.5
LAD, LCA and R	7	4	3.1
LAD only	48	32	17.7
LAD with			
LCA	13	7	8.5
R	28	16	16.8
LCA and R	28	16	22.8
LCA only	6	3	5.1
LCA with R	7	4	8.5
R only	17	9	10.5

Clinical data were recorded on admission for coronary arteriography according to principles described earlier (8). The patients' ages ranged from 15 to 72 years. The mean age was 40 years for patients with normal vessels, 51 years for those with irregularities at most 50 years for those with obstructions and 49 years for those with unclassifiable arteriograms. Using the same classification of arteriographic findings, the ratios of men to women were 2.2, 2.0, 3.7 and 3.5 respectively.

## METHODS

All coronary arteriograms were performed using a semiselective injection described by Paulin (16). The validity of this method has been tested by clinical and arteriographic evaluation of 192 patients (16) and by comparison with postmortem findings (8).

The arteriographic changes were evaluated and classified directly after the examination according to criteria described by Paulin (16). No further re-evaluation was made for this study. The arteriograms were analyzed with regard to the degree of obstructive lesions and their distribution in the four major segments of the coronary arterial tree: the right coronary artery (R), the main stem of the left coronary artery (M), the left anterior descending artery (LAD) and the left circumflex artery (LCA).

The arteries were classified with regard to the degree of

pathology as follows: 1) No demonstrable irregularities without demonstrable stenosis 2) Stenosis with diameter encroachment of 1/4 without demonstrable delay of contrast filling distal to the stenosis 3) Occlusion filling distal to the stenosis 4) Stenosis with demonstrable delay of contrast filling distal to the stenosis 5) Occlusion.

Changes of grades 3-5 were designated as lesions. When patients or arteries were classified to the degree of arterial lesions 2-5, the least one lesion in a subgroup did not exclude lesions of a lower degree in the same patient. In 94 examinations the arteriograms were of high quality to allow satisfactory assessment of the coronary arterial tree and were therefore classifiable.

The census registry was used to give an estimate among all patients up to June 1, 1973. The causes of death was obtained from death certificates. The prevalence of autopsy was about 40%.

The statistical significance of differences in values was determined by Student's  $t$  test and numbers by the  $\chi^2$  test. Values of  $p < 0.05$  were significant.

## RESULTS

### Extent and severity of arteriographic

One hundred and twenty-eight patients had normal arteriograms. 85 (17%) had at least one obstruction and 179 (37%) had obstructions and 179 (37%) had obstructions and 179 (37%) had obstructions. The obstructions are classified in Table I and the distribution of arteriographic lesions in 179 patients (48%) had obstructions of one or more of the arteries involved were M 6%, LAD 7%, R 20%. Obstructions of two or three arteries were found in 28, 20 and 4% respectively.

Table II shows the severity of obstructions of the four main arteries. The total number of obstructed arteries in 179 patients was 122 or 1.8 per patient. The LAD alone or in combination with other arteries was the site of obstruction in 79% of these patients. The M was involved in 12%, the LCA in 36% and the R in 52% with obstructions. In the LAD obstructions of grades 3, 4 and 5 occurred about equally.

Obstructions in the M were of grade 3 in 12 patients. No patient had occlusion in the M. Obstructions found in the LCA were of grades 3, 4 and 5. Only four of 90 occlusions in the LCA, the remaining occlusions were of grades 3, 4 and 5. Taking all obstructions together the distribution of grades 3, 4 and 5 was 46%, 26% and 28% respectively.

## Distribution and degree of arteriographic obstructions in 179 patients

	No. of arteries involved				
	Left M	LAD	LCA	R	Total
observation					
without delay (grade 3)	18	44	51	35	148
with delay (grade 4)	4	51	10	19	84
late (grade 5)	0	47	4	39	90
total	22	142	65	93	322
patients	12	79	36	57	
obstructions	7	44	20	29	

## MORTALITY

the total of 486 patients 140 (29%) had died in the postarteriographic period of 7-12 years. Table III shows the relationship between arteriographic findings and causes of death. The common cause of death was coronary heart disease among patients with coronary obstructions or with unclassifiable arteriograms. Coronary deaths occurred among the 128 patients with normal arteriograms and only two (one 2 years and 8 years after arteriography) of 15 deaths among the 85 patients with irregularities at most contributed to coronary heart disease. Non-coronary heart disease, particularly cardiomyopathy and pulmonary lesions, was the cause of death among patients with normal arteriograms or irregular vessels.

For 486 patients the clinical course was available for at least seven years. It was therefore considered appropriate to analyze the mortality during the period to supplement the data given above and in Table III, which also include the patients with no follow-up. The total seven-year mortality among patients with normal arteriograms 13%

(17 out of 128) with irregularities 13% (11 out of 85) obstructions 23% (42 out of 179) and unclassifiable arteriograms 37% (30 out of 94).

The yearly mortality among patients with obstructions is shown in Table IV. The mortality was high during the first year, about 8%. It fell thereafter and remained constant at 2-3% during the following six years and then rose during the final years of observation.

## Comparison between deceased and surviving patients with obstructive coronary disease

A total of 88% of those who died and 73% of those who survived had had angina pectoris or myocardial infarction as defined earlier (8). The mean radiographic heart size, another sign of heart disease, was larger in patients who died (899 ml) than in those who survived (790 ml). The mean serum cholesterol was 295 mg/100 ml (7.67 mmol/l) in deceased patients and 306 mg/100 ml (7.96 mmol/l) in survivors. Hypertension, defined as a blood pressure of at least 160/100 mmHg, was more prevalent among non-survivors (55%) than survivors (49%).

## III Number and causes of death in June 1973 among 486 patients who underwent arteriography 1961-66

of death	Arteriographic findings			
	Normal arteries (N = 128)	Irregularities (N = 85)	Obstructions (N = 179)	Unclassifiable (N = 94)
coronary heart disease	0	2	50	76
non-coronary heart disease	15	8	2	3
	10	5	10	9
	25	15	62	38

Table IV Annual mortality among patients with obstruction at arteriography

Years after arteriography	No. of pats		Mortality (%)
	Alive at start	Dead	
0-1	179	15	8.4
1-2	164	6	3.7
2-3	158	4	3.2
3-4	153	4	2.6
4-5	149	5	3.4
5-6	144	3	2.1
6-7	141	4	2.8
7-8	117	6	5.1
8-9	82	9	11.0
9-10	47	4	8.5
10-11	40	0	-
11-12	20	1	-
12-13	1	0	-

The mean age and the proportion of males were the same in both categories (50 years and 79% respectively). The above mentioned differences did not reach statistical significance.

The seven year mortality in relation to the number of arteries obstructed is shown in Table V. None of the differences between these figures is statistically significant. In Table VI the patients are grouped according to the severity of the obstructions. The groups include patients exhibiting at least one obstruction of the stated degree of severity but do not exclude the possibility of concomitant obstruction of a lower degree of severity. The difference between mortality figures among those with stenosed and those with occluded arteries is significant.

## DISCUSSION

### Arteriographic findings

Comparison can be justified when criteria used in different studies are similar. This applies with respect to our study to that of Proudfit et al (17) who investigated 1000 patients with a prevalence of normal arteriograms in 27%. They found obstructions reducing the diameter of the artery by at least half in 59% of their series. This group of patients corresponds closely to the patients with obstructions in our study (Table I). The number of arteries obstructed per patient was 1.8 in our study and 2.0 in that of Proudfit et al (17).

The greatest difference between the two studies

is the prevalence of single vessel obstruction. LAD which was considerably more common among our patients i.e. 32 vs 17%. The same site was true for single artery obstruction in the LCA 3% of our and 5.1% of the patients in Proudfit et al. When classifying all obstructions with respect to distribution and degree of severity, we found that 21% of the lesions in the group of complete obstructions were localized to the LAD. This result diverges markedly from the findings in the occlusion group in which the corresponding figure was only 4%.

Gensini and Kelly (11) defined the severity of disease as arteriographic obstruction of at least 50% of the diameter of the vessel by 75% or more. In our series their 1263 patients 639 fulfilled this criterion. These 33% had obstructions in the LAD, the RCA and its branches only 7% in the RCA and 58% in both these vessels. When our patients with obstructions are grouped in the same way, prevalences of 42% are found. Compared to our study that of Proudfit et al (17) and Gensini and Kelly appear to have comprised a higher proportion of patients with obstructions in several vessels.

In an earlier study Gensini and Bazzucchi (12) described the angiographic findings in 1000 patients 38% of whom were judged to be without significant coronary artery disease. Among the remaining patients 68 complete occlusions were found. The distribution for the three arteries

Table V Seven year mortality in relation to number of obstructed arteries

No. of obstructed arteries	No. of pats	
	At risk	Dead
One	86	14
Two	50	14
Three or four	43	14

Table VI Seven year mortality in relation to severity of obstruction

Degree of obstruction	No. of pats	
	At risk	Dead
Stenosis without delay	52	7
Stenosis with delay	40	7
Occlusion	77	28

# VII Cardiac mortality after coronary arteriography in patients with obstructive coronary artery

Material of Webster et al (20) five year mortality was calculated from their figure 5 and in that of Brymer et al (6) from figure 1

Area and authors	Mean age at arteriography (y)	Years of observation after arteriography	Cardiac mortality (%)
Core Maryland Friesinger et al (9)	~42	5	27
Core Ohio Bruschke et al (5)	~50	5	34
		7	56
Core Ohio Webster et al (20)	~49	5	34
Core Ohio Lim et al (14)	<40	5	29
Core Michigan Brymer et al (6)	~47	5	31
Core Ontario Burggraf and Parker (7)	~50	5	27
		7	35
Scg Sweden Present study	~50	5	16
		7	20

Non-cardiac mortality Non-cardiac mortality was about 5% of this figure

6% LCA 13% and R 51% When the occlusions in our patients are grouped in the same way the figures are LAD 52% LCA 4% and R 43% In the occlusions were mainly found in the LCA while in the patients of Proudfit et al and Buonanno a larger proportion were located in the LCA and the R

Our findings differ from those reported with respect to the degree of pathologic findings and the distribution of the most severe arterial lesions The validity of these transatlantic differences calls for further studies

Ger and Stary (2) have published a study on arteriography of coronary obstructions From heart preparations obtained from autopsies performed in 14 countries 300 coronary arterial lesions with at least one stenosis obstructing the artery by more than half were selected for the study The arterial pathology was assessed by dissection and staining of the preparations Obstruction of one two three and four vessels respectively were present in 39 33 25 and 3% of the specimens For single vessel obstruction the distribution among the four main arteries was M 2% L 67% LCA 13% and R 18% The mean number of obstructions per patient was 1.9 The lesions of all obstructions were M 7% LAD 44% L 20% and R 29% These prevalence figures agree remarkably well with those found in the present study (Table II)

Rodriguez et al (18) studied 430 hearts using an injection technique They devoted special interest

to the presence of occlusions and found a total of 227 with a distribution of LAD 34% LCA 26% and R 39% A higher proportion of occlusions was thus found in the LCA than in the in vivo studies Schlesinger and Zoll (19) found similar results in earlier postmortem studies using a similar injection technique These results may indicate that an occlusion is particularly deleterious if it involves the LCA

## Mortality

Cardiac mortality is the factor with the highest variability within individual studies and between different studies We have therefore chosen to deal mainly with this variable

The high early mortality is not due to arteriographic complications (8) being a common phenomenon in series of patients with progressive disease The increasing late mortality is probably due to an accelerated incidence of coronary heart disease at higher ages

Patient series followed for at least five years after arteriography have been reported from the USA (5 6 9 14 20) and from Canada (7)

Although the above mentioned studies may seem to have provided enough information the present study was undertaken for the following reasons First studies of this type have not been published from Europe Epidemiologic studies have demonstrated differences concerning the prevalence and prognosis in coronary heart diseases especially between Sweden and other similar countries It is



therefore of interest to analyze groups of patients whose coronary artery disease is arteriographically defined. Secondly the selection of our patients was not influenced by surgical considerations or operations either at the time of arteriography or during the subsequent observation time.

Table VII presents the published studies with long term follow up and compares the cardiac mortality in patients with obstructive coronary artery disease at five and seven years after arteriography. The age and sex compositions of the different studies are similar: the proportion of men varies between 73 and 90% and the mean age between 42 and 50 years. An exception is the study from Cleveland (14) which comprises exclusively men below 40 years of age.

In our study the calculation of cardiac mortality was based on all 179 patients with obstructions. The total number of deaths is summarized at five and seven years in Table IV. Six and seven non cardiac deaths respectively were subtracted from these figures. Among patients with unclassifiable arteriograms in our study the cardiac mortality at five and seven years was only slightly higher: 18% and 26% respectively, which should not significantly bias the figures of patients with obstructions.

Table VII shows that the agreement among the four North American regions concerning five year mortality is good. The mean value was about 30% while in our study it was only half: 16%. The seven year mortality was highest: 46% in the Cleveland study (5) and only one third as high in Göteborg: 20% while the Canadian study (7) reported an intermediate figure of 35%. These differences in mortality are interesting although difficult to explain. It might be questioned whether our arteriographic technique which is non selective gives a correct picture of the coronary arterial tree. However one would have to postulate a significant overreading of vascular pathology in our material to account for the differences and such a postulate is in complete opposition to the assumption that non selective arteriography should have a lower yield than selective angiographic examinations. Furthermore the validity of our technique has been verified in a previous study (8).

The differences in mortality are remarkable in relation to the relatively small differences in arteriographic pathology five and seven years previously.

A considerable number of patients were excluded from the North American studies owing to coronary

surgery after arteriography. This may lead to a concentration of patients with severe damage and a poorer prognosis in the parts of the materials on which the analyses are based (5). The results may also differ because of differences in the natural history of the disease in different countries. This is suggested by the figures on cause of death presented by the official statistics of the American life expectancy. Thus Björkling (9) points out that the mortality for men from all causes from coronary heart disease in the US and Sweden for 1963-64 differed considerably: at the age of 50 years for example it was 2.3% for the American population. It is of great interest that differences between the US and Sweden regarding prognosis rather seem to be on the state of the myocardium as the coronary artery pathology seems to be similar.

Comparisons of the prevalence of factors such as myocardial infarction, hypertension, other cardiovascular risk factors at the time of arteriography are rendered difficult by differences concerning the definition of these factors.

We found that age, sex, hypertension, cholesterol values registered at the time of arteriography had no influence on the death among patients with obstructions. The prevalence of obesity, smoking and glucose tolerance had been found to be of little or no predictive value (12, 15). Previous myocardial infarction has not been found to be of predictive value either in our study or in previous studies of patients with arteriographically demonstrated atherosclerosis (5, 7, 12, 15, 20).

The prognosis is of course poorer in patients with severe myocardial damage and poor compensation shown as cardiac enlargement demonstrated by ventriculography (5). The measurement of the pressure in the left ventricle in long term studies including our own in which the measurement after coronary arteriography has been found to indicate that the arteriogram itself contains important information with respect to the prognosis (5, 6, 7, 9, 14, 15, 20). In our patients the mortality during a period of seven years after arteriography was twice as high in patients with three or four obstructed arteries compared with patients in whom only one artery was obstructed. In patients with at least one artery occluded had a

e mortality of those who had no obstruction were than stenosis without delay. The finding only the latter difference is statistically significant suggests that it is the degree of the obstruction rather than the number of arteries obstructed which is of importance for the prognosis. The majority of patients with advanced disease of the vessels survived however five years or after arteriography. Atherosclerosis of the epicardial arteries thus seems to be only one of the components in a complex interplay of vascular, humoral and myocardial factors. Under certain circumstances lead to clinical disease or sudden death.

A normal arteriogram in the absence of non-coronary heart disease meant a good prognosis despite the absence of pain or acute serum enzyme and ECG abnormalities suggestive of myocardial infarction. The arteriography. No cardiac death due to myocardial infarction occurred in these patients during the subsequent 7-12 years. This finding is in agreement with the results of previous studies (1, 2, 9, 13, 15). Patients with only wall motion abnormalities had almost as good a prognosis as found in a previous study by others (4). Coronary arteriography is thus of great prognostic value in the prediction of the outcome for middle aged patients with chest pain of unclear etiology.

#### ACKNOWLEDGEMENTS

This study was supported by grants from the Swedish Medical Association against Heart and Chest Diseases, the Association of Senior Physicians in the Southern Alvsborgs County, Sweden.

#### REFERENCES

- 1 Miller C R, Pepine C J & Rogers A K. Long term observations in patients with angina and normal coronary arteriograms. *Circulation* 48: 36, 1973.
- 2 Berger R L & Stary H C. Anatomic assessment of atherosclerosis by the saphenous vein bypass operation in coronary artery disease. *N Engl J Med* 285: 248, 1971.
- 3 G. The biology of myocardial infarction. *Circulation* 37: 1071, 1968.
- 4 Buschke A V G, Proudfit W L & Sones F M. Clinical course of patients with normal and slightly or moderately abnormal coronary arteriograms. *Circulation* 48: 936, 1973.

- 5 — Progress study of 590 consecutive nonsurgical cases of coronary disease followed 5-9 years. *Circulation* 48: 1147, 1973.
- 6 Brymer J F, Buter T H, Walton J A & Willis P W. A natural history study of the prognostic role of coronary arteriography. *Am Heart J* 88: 139, 1974.
- 7 Burggraf G W & Parker J O. Prognosis in coronary artery disease. *Circulation* 51: 146, 1975.
- 8 Forsberg S Å, Alestig K, Bjure J, Haggendahl E, Paulin S, Varnauskas E & Werkö L. Post mortem coronary arteriographic, clinical and electrocardiographic findings in 80 patients investigated with coronary arteriography. *Acta Med Scand* 189: 463, 1971.
- 9 Friesinger G, Page E E & Ross R S. Prognostic significance of coronary arteriography. *Trans Am Physicians* 83: 78, 1970.
- 10 Gensini G G & Buonanno C. Coronary arteriography. A study of 100 cases with angiographically proved coronary artery disease. *Dis Chest* 54: 90, 1968.
- 11 Gensini G G & Kelly A E. Incidence and progression of coronary artery disease. An angiographic correlation in 1263 patients. *Arch Intern Med* 129: 814, 1972.
- 12 Humphries J O, Kuller L, Ross R S, Friesinger G C & Page E E. Natural history of ischemic heart disease in relation to arteriographic findings. *Circulation* 49: 489, 1974.
- 13 Kemp H G, Vokonas P S, Cohn P F & Gorlin R. The anginal syndrome associated with normal coronary arteriograms. *Am J Med* 54: 735, 1973.
- 14 Lim J S, Proudfit W L & Sones F M. Selective coronary arteriography in young men. *Circulation* 49: 1122, 1974.
- 15 Oberman A, Jones W B, Riley C P, Reeves T J, Sheffield L T & Turner M E. Natural history of coronary artery disease. *Bull NY Acad Med* 48: 1109, 1972.
- 16 Paulin S. Coronary angiography. A technical, anatomical and clinical study. *Acta Radiol (Suppl)* 233, 1964.
- 17 Proudfit W L, Shirey E K & Sones F M Jr. Distribution of arterial lesions demonstrated by selective cine-coronary arteriography. *Circulation* 36: 54, 1967.
- 18 Rodriguez F L, Robbins S L & Banasiewicz M. Postmortem angiographic studies on the coronary arterial circulation. *Am Heart J* 68: 490, 1964.
- 19 Schlesinger M J & Zoll P M. Incidence and localization of coronary artery occlusions. *Acta Pathol* 32: 178, 1941.
- 20 Webster J S, Moberg C & Rincon G. Natural history of severe proximal coronary artery disease as documented by coronary cineangiography. *Am J Cardiol* 33: 195, 1974.

# The very journals for you!

## **Acta Chirurgica Scandinavica**

Editor L. Thoren

8 issues per volume Free supplements. Including free subscriptions to the *Scandinavian Journal of Plastic and Reconstructive Surgery* (without suppl) the *Scandinavian Journal of Thoracic and Cardiovascular Surgery* (without suppl) and the *Scandinavian Journal of Urology and Nephrology* (without suppl) Together 17 issues per year

Current volume 145/1979

Sw kr 420 per year incl postage

## **Acta Dermato-Venereologica**

Editor Nils Thyresson

6 issues per volume Free supplements

Current volume 59/1979

Sw kr 190 per year incl postage

## **Acta Medica Scandinavica**

Editor J Waldenström

6 issues per volume Free supplements

Current volumes 205-206/1979

Sw kr 375 per year (two volumes) incl postage

## **Acta Oto-Laryngologica**

Editor C.-A. Hamberger

6 issues per volume Free supplements

Current volumes 87-88/1979

Sw kr 300 per year (two volumes) incl postage

## **Acta Pædiatrica Scandinavica**

Editor R. Zetterström

6 issues per volume Free supplements

Current volume 68/1979

Sw kr 300 per year incl postage

## **Scandinavian Audiology**

Editor Stig Arlinger

4 issues per volume Free supplements

Current volume 8/1979

Sw kr 175 per year incl postage

## **Scandinavian Journal of Infectious Diseases**

Editors Justus Ström and Sten Winblad

4 issues per volume Free supplements

Current volume 11/1979

Sw kr 175 per year incl postage

## **Scandinavian Journal of Plastic and Reconstructive Surgery**

Editor Bengt Johanson

3 issues per volume Free supplements

Current volume 13/1979

Sw kr 185 per year incl postage

## **Scandinavian Journal of Psychology**

Editor Lars Kebabian

4 issues per volume

Current volume 20/1979

Sw kr 170 per year incl postage

## **Scandinavian Journal of Rehabilitation Medicine**

Editor Olle Hoök

4 issues per volume Free supplements

Current volume 11/1979

Sw kr 150 per year incl postage

## **Scandinavian Journal of Rheumatology**

Editor Veikko Laine

4 issues per volume Free supplements

Current volume 8/1979

Sw kr 150 per year incl postage

## **Scandinavian Journal of Social Medicine**

Editor Ragnar Berfvenstam

3 issues per volume Free supplements

Current volume 7/1979

Sw kr 140 per year incl postage

## **Scandinavian Journal of Thoracic and Cardiovascular Surgery**

Editor Viking Olov Björk

3 issues per volume Free supplements

Current volume 13/1979

Sw kr 185 per year incl postage

## **Scandinavian Journal of Urology and Nephrology**

Editor Åke Fritjofsson

3 issues per volume Free supplements

Current volume 13/1979

Sw kr 185 per year incl postage

## **Uppsala Journal of Medical Sciences**

Editor Gunnar Ågren

3 issues per volume Free supplements

Current volume 84/1979

Sw kr 100 per year incl postage

Swedish subscribers Add V A T to all prices

Free inspection copies on request—write to

**The Almqvist & Wiksell Periodical Company**  
Box 62, S-101 20 Stockholm, Sweden

# Sick Sinus Syndrome Treated with Permanent Pacemaker in 109 Patients

## A Follow Up Study

Kjell Breivik Ole Jørgen Ohm and Leidulf Segadal

From Medical Department A and Surgical Department University of Bergen  
School of Medicine Bergen Norway

**ABSTRACT** During the last decade implantation of pacemakers has become the treatment of patients suffering from the sick sinus syndrome (SSS). We have followed up 112 SSS patients with permanent pacemakers in Haukeland Hospital in the period 1966-76. The pacemakers were removed from three of the patients. In the remaining 109 patients the SSS was characterized by bradyarrhythmias (TBA) in 44 and bradyarrhythmias (BA) in 65. Before implantation, 68 patients had syncope and 27 severe dizziness. After implantation, symptomatic improvement was apparent in all patients; only three still had syncope. During follow up period (mean 34.4 months), 29 patients died (yearly mortality 9.3%). There was no significant difference in total mortality between patients with TBA and with BA. Concomitant disturbances in atrioventricular (AV) conduction occurred in 35.8% of patients. Among 79 of 80 patients still alive, 19 had developed total AV block, 19 had stable atrial fibrillation, 12 of these were possibly pacemaker induced (ventricular rate >60/min). Systemic embolism was observed in 16 patients, more frequently in the TBA (12/44) than in the BA group (3/65) ( $p < 0.001$ ). It is concluded that permanent pacemakers have an excellent symptomatic effect in patients with SSS. The prognosis is mainly determined by the presence or absence of coronary heart disease and/or heart failure.

**Key words:** sick sinus syndrome, pacemaker treatment, prognostic factors.

Acta Med Scand 206 153-159 1979

In recent years much of the rapid growth in the use of pacemaker treatment can be attributed to the increasing treatment of patients suffering from sick sinus syndrome (SSS). Although most reports report a favourable symptomatic improvement in their patients (3, 11, 13-16, 18, 24), reports

on the prognosis of the same patients despite pacemaker therapy have been rather depressing (3, 10, 14, 16).

For these reasons we decided to review the patient material in our clinic with special emphasis on etiology of the rhythm disturbances, prognostic factors, morbidity after implant and the further development of the rhythm disturbances.

## PATIENTS

Between 1966 and 1976 a total of 112 patients with SSS had permanent pacemakers implanted. Three patients' pacemakers were removed after 13, 45 and 7 months because of wound infections and skin perforations in the former two, who were considered pacemaker independent at the time of explantation. The third patient demanded to have her pacemaker removed after seven months because she felt it did not improve her condition. The first patient died from pneumonia 38 months after removal. The two others are still alive, 55 and 12 months after explantation.

The remaining 109 patients were followed up until December 1977, i.e. for 13-106 months or until death (mean 34.4 months) or for a total of 3755 observation months (312.9 years).

The study comprised 61 males (age range 4-88 years (mean 66.2)) and 48 females (age range 40-90 years (mean 68.4)). Mean age of the total study population was 67.2 years, or about 3 years less than in our patient series with atrioventricular (AV) block (17). All fulfilled Ferrer's (8) criteria for SSS. There was a preponderance of males in the bradyarrhythmia (BA) group (43 ♂, 22 ♀) and a slight female dominance (26 ♀, 18 ♂) in the tachy bradyarrhythmia (TBA) group. There was no significant age difference between the BA and TBA groups.

**Abbreviations:** SSS=sick sinus syndrome, AV=atrioventricular, BA=bradyarrhythmia, TBA=tachy bradyarrhythmia, CHD=coronary heart disease, TGA=transposition of the great arteries, CWS=chest wall stimulation, AF=atrial fibrillation, SR=sinus rhythm.

Table 1 *Etiology of rhythm disturbances in the total study population of 109 patients*

	<i>n</i>
Primary arrhythmia	47
CHD	33
Rheumatic valve disease	11
Rheumatic heart disease (without valve lesion)	1
Hypertension	5
Endocrine disorders	4
Cardiomyopathies	3
Collagen diseases	3
Constrictive pericarditis	1
TGA	1

The etiology of the rhythm disturbance is shown in Table 1. Primary rhythm disturbance was assumed to exist when no other etiological factor could be found. Coronary heart disease (CHD) defined as previous myocardial infarction (clinically or on ECG evidence) or a history of angina pectoris showed a male dominance of 23/33. Sixteen patients had a history of previous infarction. Patients with rheumatic heart disease with or without valve lesion had a history of previous rheumatic fever. Hypertension was defined as diastolic BP exceeding 95 mmHg or need of antihypertensive medication. Two of four patients with endocrine disorders were hypothyroid, one was hyperthyroid and one had tuberculosis and Addison's disease. All three cardiomyopathies were congestive. Two of the patients with collagen disease had polymyalgia and one had rheumatoid arthritis. Our youngest patient was a 4-year-old boy with operated transposition of the great arteries (TGA).

(68 patients) and dizziness/near syncope patients) were the main indications for implanting a pacemaker. Nine patients received pacemakers because of serious heart failure with slow rhythms, three had TGA that could not be controlled by medication alone and two occasionally had extreme bradycardia down to 20 beats/min with anginal attacks. Other symptoms noted were palpitations (35 patients), heart failure (29 patients) and exertional dyspnea (30 patients). The 109 patients were grouped according to the New York Heart Association as follows: class I 27 patients, class II 57, classes III-IV 25 patients.

The heart size was normal in 59 patients, enlarged in 50. The cardiothoracic ratios exceeding 0.5 or relative heart volumes exceeding 550 ml/m<sup>2</sup> in males and 450 ml/m<sup>2</sup> in females.

## METHODS

The rhythm disturbances were documented by repeated 12-lead ECG recordings, telemetry or provocative tests like sinus node recovery time or carotid sinus pressure.

When more than one arrhythmia was present, the dominant one is listed. AV conduction defects were found from repeated ECG recordings at the time of pacemaker implantation. Conduction defects from digitalis or antiar-

rhythmic drug toxicity and electrolyte disturbances were excluded.

All pacemaker implantations were performed in the Surgical Department, Haukeland Hospital. The subcutaneous implantation route was preferred in all cases. The boy with TGA for whom a myocardial electrode was chosen. One patient with congestive cardiac failure probably diphtheric and gross cardiac enlargement was changed to a myocardial electrode because of unsatisfactory electrode position. Three patients were equipped with rate pacemakers, 97 with QRS-inhibited and 1 with QRS-triggered pacing from an atrial site. All were employed.

Our follow-up study covers all 109 patients. One patient died postoperatively from ventricular fibrillation that occurred during catheter manipulation. The patients were followed at regular three-month intervals in the Outpatient Clinic. Twenty-five patients were regularly controlled in local hospitals or by 10 doctors who consulted us if problems arose. Ten patients were performed in our hospital. Three have moved out of the region, but their doctor's request supplied the information needed.

We have been able to study the development of rhythm disturbance and conduction defect after pacemaker treatment in 79 of the 80 patients. ECGs were recorded at least twice during the months of the study at three-month intervals. In 10 patients with exclusively pacemaker rhythm or a pacemaker and spontaneous heart activity, continuous stimulation (CWS) was performed to study the heart rhythm. In five patients living far from the hospital, CWS was performed only once. At the time of the study we did not have access to 24-hour tape monitoring, therefore the rhythms are listed as stable if they were stable at more check-ups over more than a three-month period.

Of the 21 patients who died in hospital, 11 were autopsied. Detailed examination of the atria and conduction systems has not been made. For patients who died outside hospital, the cause of death has been obtained from official death certificates. Concerning the patients who died suddenly outside hospital, we interviewed close relatives when possible or the doctor who had signed the death certificate.

Fisher's Irwin test for two-by-two tables (17) was used for statistical analysis.

## RESULTS

### Morbidity

Of the 109 patients, 104 (95.4%) experienced a marked improvement of their symptoms. The most marked improvement was in patients with syncope. The most stable results were found in patients with syncope and dizziness. Syncope persisted in only three patients—two males with CHD who both died suddenly (both autopsied) and one female with postural hypotension. Four patients complained of dizziness—two of them had

## II Drug treatment before and after permanent pacemaker implantation

	Before (n)	After (n)
sinus	40	70
sympathetic drugs/ $\beta$ blockers	20	7
thrombolytic/anticholinergic	39	1
cardiac	28	35
regulators	1	3

one died from infarction after three months  
from metastasizing carcinoma of the pros-  
tate whether also cerebral is not known

two patients with extreme bradycardia and  
attacks lost their symptoms. Two of the  
patients classified as unchanged belonged to  
clinical classes III-IV. Most patients with heart  
disease experienced some improvement perhaps  
because of the more liberal use of digitalis  
medication after pacemaker implantation. Drug  
treatment before and after permanent pacemaker  
implantation is specified in Table II. The seven  
patients still on antiarrhythmic drugs were TBA  
patients in whom the arrhythmia could not be con-  
trolled by pacemaker/digitalis therapy. One female  
patient with orthostatic hypotension is still on sym-  
ptomatically.

Five patients (27.2%) in the TBA group had a  
total of 17 embolic episodes, nine of which took  
place before pacemaker implantation. Three pa-  
tients experienced their embolic episodes after im-  
plantation and five both before and after. Two died

one from pulmonary and one from intestinal em-  
bolism both were autopsied. For the remainder the  
diagnosis of the embolization was established on  
clinical grounds alone.

Only four (6%) of the patients in the BA group  
had embolic episodes in contrast to 27.2% in the  
TBA group. The difference is highly significant  
( $p < 0.001$ ). Four of the patients who experienced  
embolic episodes had valvular heart diseases, one  
of them was on anticoagulant treatment. Eight more  
patients had cardiac enlargement with involvement  
of the atria. Only four patients had normal heart  
size.

## Rhythm studies

At first implant, 39 patients (35.8%) had concomi-  
tant disturbances in the AV conduction (Table III)  
with no great difference between the BA and TBA  
groups.

The dominant rhythm at follow up in relation to  
rhythm disturbance before implantation is shown in  
Table IV. Of the five patients who later developed  
total AV block, two had signs of trifascicular dis-  
ease and three intermittent AV block II-III at the  
time of implant. Four patients with intermittent AV  
block II-III showed only pacemaker rhythm at fol-  
low ups. Three of them died before our study  
started, the fourth is confined to bed in a nursing  
home and is the only one alive whom we have not  
been able to follow up.

Nineteen (24.1%) of the 79 patients studied had  
developed stable atrial fibrillation (AF). Two addi-  
tional patients had AF at follow up, but as we were

## III Rhythm disturbances before pacemaker implantation

sinus arrest SA = sinus arrest HCS = hypersensitive carotid sinus AVJR = atrioventricular junctional  
n CSR = coronary sinus rhythm SB = sinus bradycardia IM = intermittent RBBB = right bundle branch block  
(bifascicular) = left bundle branch block (LBBB) or AV block I + RBBB TFAS (trifascicular) AV block I +  
or AV block I + RBBB + left anterior hemiblock

Dominant rhythm before (n of pats)		Concomitant AV conduction defect (no. of pats)					
		AV block I	RBBB	BFAS	TFAS	IM AV block II-III	Total
Group							
BA SA HCS	49	65	5	2	5	3	6
JR CSR	7		1				
	9		1				
							24
group							
	44	3	1	4	1	6	15
	109	10	4	9	4	12	39

Table IV Heart rhythm at follow up compared with rhythm disturbances at implantation in 79 survivors

Original rhythm disturbance		Heart rhythm at follow up					
		AF		TBA	BA	SR >60/min	AV block III
		<60/min	>60/min				
BA	47	1	2	1	27	14	2
TBA	32	6	10	3	5	5	3
Total	79	7	12	4	32	19	5

able to perform CWS only once their rhythms are not listed as stable. In the TBA group 16 (50%) of 32 patients had developed AF vs three (6.8%) of 47 in the BA group, a highly significant statistical difference ( $p < 0.0001$ ). These three patients in the BA group had enlarged hearts at implantation with involvement of the left atrium.

We did not find any significant difference in the mean observation period between those who did and those who did not develop stable AF in the TBA groups (40.4 vs 39.1 months). Ventricular rates were above 60/min in 12 of the patients with stable AF and should theoretically be managed on digitalis/antiarrhythmic treatment alone. Decision not to replace the pacemaker was made only once. The patient concerned has now been followed for three months.

#### Mortality

Twenty nine patients (26.7%) died during the follow-up (Table V) giving a yearly mortality rate of

9.3%. The mean age of the patients who died was 69.8 years (males 68.3, females 72.2). The difference in sex linked mortality in the 31% males and 10/48 (20.8%) females is male excess mortality, may be due to the prevalence of and mortality from CHD in males. Compared to the total study population we found a significantly higher mortality, 18% vs 33% among CHD patients ( $p < 0.001$ ). Twelve deceased CHD patients were males, 10 with history of previous myocardial infarction.

There was no significant difference in mortality between the TBA group, in which 1 of 44 died, and the BA group, in which 1 of 65 patients died. The BA and TBA groups are comparable since the number of deaths in patients with CHD in the BA group is larger than in the TBA group, 12 vs 3 patients (Table V).

Nineteen (38%) of 50 patients with a heart size and 11 (44%) of 25 patients in classes III-IV died. Both these groups have

Table V Mortality

Primary = primary cause of rhythm disturbances. Collagen = collagen disease. CP = constrictive pericarditis. aortic stenosis. MS = mitral stenosis.

	BA group	TBA group
Cardiovascular		
Sudden death	4 (3 CHD, 1 AS)	3 (2 CHD, 1 MS)
Acute myocardial infarction	3 (3 CHD)	4 (2 Primary, 1 CHD, 1 Coll)
Chronic heart failure	3 (3 CHD)	1 (Primary)
Ventricular fibrillation	1 (CHD)	0
Cerebral stroke	3 (2 CHD, 1 Primary)	0
Pulmonary embolism	0	1 (Primary)
Intestinal embolism	0	1 (Primary)
Total	14	10
Cancer	3 (1 Primary, 1 Collagen, 1 CP)	0
Pneumonia	0	2 (1 Primary, 1 MS)
Total	17	12

tly poorer prognosis than the whole series ( $p < 0.01$ )

Of the eight patients with all these three major factors seven died after a mean observation of 15 months (range 0-47). One patient is alive after 35 months. Rheumatic valve disease does not seem to have any major effect on prognosis. One died (30.3%) nor did the cardiomyopathies

Of the three (10%) of 30 patients with primary sinus node disturbance and no signs of heart enlargement or functional deterioration beyond class II. This gives a yearly mortality rate of 3.5% reduced to 2.7% in the Norwegian population adjusted to sex and age (5).

The major cause of death (82.8%) was cardiovascular (Table V). Of the seven patients who died suddenly and unexpectedly five had advanced aortic and one mild mitral valve disease.

All seven patients died outside hospital and the causes of the sudden deaths are not known.

Two autopsies were performed and added to CHD with previous infarction was diagnosed in both cases. No new infarctions were found. Our pacemakers functioned normally. One assumes that the cause of death was cardiac arrhythmias. The two patients who died from embolic episodes belonged to the TBA group and were treated. Three patients in the BA group died from cerebral strokes. They were autopsied and none had emboli.

## DISCUSSION

Of 1971 patients with SSS constituted only 10% of our patients treated with permanent pacemakers (16). With the introduction of demand pacemakers and a better understanding of the seriousness of the syndrome this percentage has increased to 40.5 during 1972-76. Other authors report percentages of 11.5-47 (11, 13, 18). The seriousness of the SSS is reflected by the fact that 8% of our patients had had Adams Stokes attacks. Another 24.8% were severely incapacitated by dizziness/near syncope. Forty-nine patients (45%) had a temporary pacemaker implanted because of life threatening symptoms.

There seems to be no general agreement about which diseases are of etiological importance for the SSS disorder. Davies and Pomerance (6) have demonstrated degenerative changes in the atria and

sinus node starting at the age of 60 which may explain a primary cause of the disease. Our figure of 43.1% (Table I) agrees well with that of Shaw and Kekwick (21) who reported primary arrhythmia in 47% of their patients. Others have considered CHD the most important etiological factor (11, 23) with figures ranging from 24 to 61%. The incidence of rheumatic heart disease varies from 11 to 20% (20, 21) and some authors have found a relatively high incidence of diphtheric cardiomyopathies (19, 21).

There are divergent opinions on sex distribution (10, 11, 13, 17, 19, 23) probably because the patient groups are small. We found a small male dominance of 61/48 which corresponds well with 2/1 found by Shaw and Kekwick (21) among more than 400 patients with suspected or established SSS.

Like most authors (10, 11, 13, 17, 19, 21, 22) we noticed an excellent improvement of complaints like syncope and dizziness. Residual complaints could be explained by coexisting diseases not related to sinus node dysfunction. The effect on heart failure was less convincing possibly because of the loss of atrial contribution.

The occurrence of systemic emboli has been a controversial matter. Fairfax et al (7) found embolic episodes in 20% of patients with TBA vs 4% of patients with BA and in 13% of patients with AV blocks. Bathen et al (4) found embolic episodes in 35% in the TBA group, 7% in the BA group and 10% in the AV group. Some authors report 21-48% in TBA patients (3, 17) while some others (10) found no embolic episodes in 50 patients with BA. There is an uncertainty regarding these studies as the diagnosis of embolic episodes is given in most cases on clinical grounds alone but as the authors point out the bias would at least be the same in all groups. We have also found a significantly higher incidence of suspected embolic episodes in our TBA patients 27.2% vs 6% in the BA group. In our AV block series (17) we found a mortality of 5% from pulmonary embolism while 10% died from cerebral stroke. The latter figure corresponds with that found in this study. Bathen et al (4) found that 10 out of 14 embolic episodes occurred after pacemaker implantation. Radford and Julian (18) on the other hand found that 8 out of 10 embolic episodes occurred before pacemaker implantation. Embolic episodes before and after implantation were more equally divided in our series (9 before, 8 after).

All the papers quoted indicate that the



mechanism of the embolic episodes can be attributed in most instances to changes between tachy- and bradyarrhythmia. It seems therefore desirable to follow these patients closely in the immediate postoperative period in order to find the best antiarrhythmic regimen. Whether this should be preferred to permanent anticoagulant treatment needs to be further elucidated. Four of our patients had valvular heart disease for which the indication for an anticoagulant therapy had already been established. One patient with aortic valve prosthesis in the BA group nevertheless had an embolic episode although he was on adequate anticoagulant therapy. Another eight of the 16 patients had enlarged heart with involvement of the atria and only four had normal heart size. At the moment we do not give prophylactic anticoagulant therapy routinely to our TBA patients. We are led to believe that anticoagulants should be given only to patients with heart valve disease or enlarged heart and not routinely as recommended by some authors (4, 7, 18). Only a prospective study, however, can give a more definite answer to this question.

Little is known about the natural course of the SSS. Ferrer (8) states that it probably takes 5–10 years before the sinus node is completely destroyed by degeneration. Amikam and Riss (2) define three different forms: 1) a subacute with TBA, CHD and poor prognosis; 2) a transient with spontaneous cure by development of stable AF, equally divided between TBA and BA groups; 3) a chronic with no CHD and good prognosis.

This is in contrast to our experience. We found the highest incidence of CHD in the BA group, which would have an unfavourable effect on prognosis. Furthermore, we found that the tendency to develop stable AF was more pronounced in the TBA group (Table IV). This seems to indicate that TBA may be considered the transient form of the syndrome. Of 56 patients with BA reported by Vera et al. (23), 11 have developed stable AF after a mean observation period of 3.2 years. Those who did not develop AF were observed for a much shorter period (1.9 years) than those who did (5.5 years). Ten of the patients are now considered pacemaker-independent. There was no great difference in observation periods between those who did and those who did not develop stable AF in our TBA group. Twelve of our 19 patients who developed stable AF had adequate ventricular response ( $>60/\text{min}$ ) and may now be considered pacemaker-independent.

Studies with Holter monitoring now in progress may throw more light on this point.

Narula (15) found that 67% had conduction defects in a patient group with bradycardia. Our figure of 35.8% corresponds with that of Härtel and Talvensaan (12). There seems to be a significant overlap between and the AV conduction defects.

Theoretically it would be ideal to establish pacing. Some authors (9) claim that AV sequential pacing would be beneficial in 77% of the treated patients. The great number of rhythm disturbances may, however, be a justification to a more liberal use of atrial pacing. In single cases AV synchrony may be critical due to a marked fall in cardiac output (11), recently shown (1) due to atrial reflex relaxation of peripheral resistance.

AV sequential pacing is indicated for patients. Because of the complexity of pacemakers, they should only be implanted after thorough hemodynamic investigations. If, without heart failure, we have instead of a programmable ventricular low rate pacemaker, thus saving the patients from syncope and allowing their hearts to work in a physiological way, the time.

Death rates differ widely between studies (22, 24) but are hard to compare as the indications for implanting pacemakers also differ from clinic to clinic. We found that the patients in the earliest years of implantation had a better prognosis than those from the later years, probably due to a more liberal use of pacemaker treatment and more critically ill patients in recent years. We found a yearly mortality rate of 9.3% and in the first year it was 9.2% (10/109). We noted a high incidence of unexpected sudden death—7/15 vs. 11/60 (18%) in our AV block study. This may be ascribed to the higher incidence of SSS than in AV block patients (17, 18) and that pacemaker treatment does not protect from probable cardiac arrhythmias.

Like Skagen and Fischer-Hansen (22), we found that when we subdivided our patients into two groups—one with CHD and/or serious heart or cancer and one without—the yearly mortality rate in the latter group was close to that of the age-adjusted Norwegian population. This seems to confirm that SSS per se is no prognostic factor.

## CONCLUSION

ents with SSS now account for almost half of patients in our pacemaker clinic. 2) Stable AF is a spontaneous cure of SSS. TBA seems to be the intermediate form of the syndrome. 3) Pacemaker implantation has an excellent effect on dizziness and lightheadedness but only minor effect on fatigue. 4) CHD is more frequent among patients with SSS than with AV block, a factor which may influence life expectancy. Coexisting heart failure and not SSS per se is of importance for the prognosis. 5) Coexisting AV conduction defects are common. It will together with the development of permanent pacing from an atrial site less recommendable as a routine method. 6) Systemic embolic events are significantly more common in patients with BA than with SA. It is noteworthy that out of 100 patients with one or more embolic episodes 50 had normal heart size. Prospective studies are needed before a definite answer can be given to the question whether or not long term anticoagulant therapy will have a beneficial effect.

## REFERENCES

1. Candin C, Fouad F M, Tarazi R C, Castle L, Morant V. Three cases of hypotension and syncope with ventricular pacing. Possible role of atrial reflexes. *Am J Cardiol* 42: 137, 1978.
2. Kam S & Riss E. The natural history of sick sinus syndrome following permanent pacemaker implantation. *Circulation (Suppl)* III: 155, 1977.
3. Cohen J M, Cohen S J & Morkin E. Bradycardia-tachycardia syndrome. Results in twenty-eight patients treated by combined pharmacologic therapy and pacemaker implantation. *Chest* 66: 257, 1974.
4. J. Sparr S & Rokseth R. Embolism in sinoatrial disease. *Acta Med Scand* 703: 7, 1978.
5. Central Bureau of Statistics. Statistical year book of Norway. p. 30. Grøndahl & Søn, Oslo, 1977.
6. Veres M J & Pomerance A. Quantitative study of the changes in the human sinoatrial node and in nodal tracts. *Br Heart J* 34: 150, 1972.
7. Ruffa A J, Lambert C D & Leatham A. Systemic embolism in chronic sinoatrial disorder. *New Engl J Med* 295: 190, 1976.
8. Frier M J. The sick sinus syndrome. *Circulation* 63: 5, 1973.
9. Funke H D & Schaldach M. Eine einfach und zuverlässig im Vorhof anzubringende Herzschrittmacherelektrode. *Dtsch med Wochenschr* 103: 819, 1977.
10. Gould L, Reddy C V R & Becker W H. The sick sinus syndrome. A study of 50 cases. *J Electrocardiol* 11: 11, 1978.
11. Hartel G & Talvensaar T. Treatment of sinoatrial syndrome with permanent cardiac pacing in 90 patients. *Acta Med Scand* 198: 341, 1975.
12. Hodges I L Jr & Lehmann E L. Basic concept of probability and statistics. 2nd ed. p. 337. Holden Day, San Francisco, 1970.
13. Knutsen K M. Treatment of sick sinus syndrome associated with permanent cardiac pacing. *Tidsskr Nor Lægeforen* 98: 188, 1978.
14. Krishnaswami V & Geraci A R. Permanent pacing in disorders of sinus node function. *Am Heart J* 89: 579, 1975.
15. Narula O S. Atrioventricular conduction defects in patients with sinus bradycardia. *Circulation* 44: 1096, 1971.
16. Ohm O J. Fifteen years of cardiac pacing. *Acta Med Scand (Suppl)* 603: 23, 1977.
17. Ohm O J & Breivik K. Patients with high grade atrioventricular block treated and not treated with a pacemaker. *Acta Med Scand* 203: 571, 1978.
18. Radford D J & Julian D G. Sick sinus syndrome. Experience of a cardiac pacemaker clinic. *Br Med J* 3: 504, 1974.
19. Rasmussen K. Chronic sinoatrial heart block. *Am Heart J* 81: 38, 1971.
20. Rokseth R & Hatle L. Prospective study on the occurrence and management of chronic sinoatrial disease with follow-up. *Br Heart J* 36: 587, 1974.
21. Shaw D B & Kekwick C A. Potential candidate rates for pacemakers. Survey of heart block and sinoatrial disorder (sick sinus syndrome). *Br Heart J* 40: 99, 1978.
22. Skagen K & Fischer Hansen J. The long term prognosis for patients with sinoatrial block treated with permanent pacemaker. *Acta Med Scand* 199: 13, 1975.
23. Vera Z, Mason D T, Awan N A, Miller R R, Janzen D, Tonkon M J & Vismara L. A. Improvement of symptoms in patients with sick sinus syndrome by spontaneous development of stable atrial fibrillation. *Br Heart J* 39: 160, 1977.
24. Wohl A J, Laborde J, Atkins J M, Blomqvist C G & Mullins C B. Prognosis of patients permanently paced for sick sinus syndrome. *Arch Intern Med* 136: 406, 1976.

mechanism of the embolic episodes can be attributed in most instances to changes between tachy- and bradyarrhythmia. It seems therefore desirable to follow these patients closely in the immediate postoperative period in order to find the best antiarrhythmic regimen. Whether this should be preferred to permanent anticoagulant treatment needs to be further elucidated. Four of our patients had valvular heart disease for which the indication for anticoagulant therapy had already been established. One patient with aortic valve prosthesis in the BA group nevertheless had an embolic episode although he was on adequate anticoagulant therapy. Another eight of the 16 patients had enlarged heart with involvement of the atria and only four had normal heart size. At the moment we do not give prophylactic anticoagulant therapy routinely to our TBA patients. We are led to believe that anticoagulants should be given only to patients with heart valve disease or enlarged heart and not routinely as recommended by some authors (4, 7, 18). Only a prospective study, however, can give a more definite answer to this question.

Little is known about the natural course of the SSS. Ferrer (8) states that it probably takes 5–10 years before the sinus node is completely destroyed by degeneration. Amikam and Riss (2) define three different forms: 1) a subacute with TBA, CHD and poor prognosis; 2) a transient with spontaneous cure by development of stable AF, equally divided between the TBA and BA groups; 3) a chronic with and good prognosis.

This is in contrast to our experience. We found the highest incidence of CHD in the BA group which would have an unfavourable effect on prognosis. Furthermore, we found that the tendency to develop stable AF was more pronounced in the TBA group (Table IV). This seems to indicate that TBA may be considered the transient form of the syndrome. Of 56 patients with BA reported by Vera et al. (23), 11 have developed stable AF after a mean observation period of 3.2 years. Those who did not develop AF were observed for a much shorter period (1.9 years) than those who did (5.5 years). Ten of the patients are now considered pacemaker independent. There was no great difference in observation periods between those who did and those who did not develop stable AF in our TBA group. Twelve of our 19 patients who developed stable AF had adequate ventricular response ( $>60/\text{min}$ ) and may now be considered pacemaker independent.

Studies with Holter monitoring now may throw more light on this point.

Narula (15) found that 67% had conduction defects in a patient group with bradycardia. Our figure of 35.8% corresponds with that of Hartel and Talvensaan (17). There seems to be a significant overlap between the AV conduction defects.

Theoretically it would be ideal to establish pacing. Some authors (9) claim that AV synchrony would be beneficial in 77% of the treated patients. The great number of rhythm disturbances may, however, be an objection to a more liberal use of atrial pacing. In single cases AV synchrony may be crucial due to a marked fall in cardiac output (1), recently shown (1) due to atrial reflexes or action of peripheral resistance.

AV sequential pacing is indicated for patients. Because of the complexity of pacemakers, they should only be implanted after thorough hemodynamic investigations. In without heart failure we have instead of programmable ventricular low rate pacing, thus saving the patients from syncope and their hearts to work in a physiological way the time.

Death rates differ widely between studies (22, 24) but are hard to compare as the criteria for implanting pacemakers also differ from clinic to clinic. We found that the patients in the earliest years of implantation had a better prognosis than those from the later years, probably because of a more liberal use of pacemaker treatment and more critically ill patients in recent years. We found a yearly mortality rate of 9.3% and in the first year it was 9.2% (10/109). We noted a high incidence of unexpected sudden death—17/1160 (1.8%) in our AV block study. This may be ascribed to the higher incidence of SSS than in AV block patients (17, 18) and to the fact that pacemaker treatment does not prevent from probable cardiac arrhythmias.

Like Skagen and Fischer-Hansen (22), we found that when we subdivided our patients into two groups—one with CHD and/or serious heart disease or cancer and one without—the yearly mortality rate in the latter group was close to that of the age-adjusted Norwegian population. This seems to confirm that SSS per se is no prognostic factor.

# Aortic Valve Replacement in Elderly Patients

Ole Storstein and Leif Efskind

From Medical Department B and Surgical Department A Rikshospitalet  
University Hospital Oslo Norway

**ACT** During the years 1965-75 98 patients  
tan 65 years of age had aortic valve replace-  
our hospital 24 ball valves and 74 disc valves  
t in their aortic orifice Actuarial analysis of  
l in these patients shows that the operative  
slightly higher in elder than in younger pa  
The survival curve for the following years for  
ho had disc valve implantation runs parallel  
of younger patients while those who had ball  
aplantation showed a more rapid fall in survi  
r 3 years After 10 years only 30% of patients  
ll valve transplantation were alive

ds aortic valve surgery elderly patients  
d Scand 206 161 1979

valve replacement is a well established  
utic procedure in the treatment of severe  
valvular disease Follow up studies of pa  
perated on at Rikshospitalet Oslo for aortic  
disease have shown an operative mortality of  
l 15% and a late mortality of 10% (11) In  
ears the operative mortality has fallen to 11%  
These figures must be weighed against the  
prognosis for patients with severe aortic  
is associated with ominous symptoms like  
pectoris paroxysmal dyspnea and syncope  
tic valve disease and especially aortic ste  
ws an increasing incidence with increas  
This is partly due to the pathoanatomical  
occurring in congenital bicuspid aortic  
with increasing age and partly due to the  
form of aortic stenosis which is seen  
patients with increased fibrosis and calci  
of aortic valves

hospitals there has been a reluctance to  
on elderly patients more than 65 or 70 years  
5) The reason for this has been a fear of high  
lity both at operation and in the following

years Others are of the opinion that elderly patients  
should be offered the same possibility of treatment  
as younger ones (1 2 9)

## PATIENTS AND METHODS

To study this problem we have reviewed patients more  
than 65 years of age who have had aortic valve replace-  
ment at Rikshospitalet Oslo Altogether 98 patients 62  
men and 36 women have been operated on during 1965-  
75 Twenty four of these had ball valve implantation in  
most cases Starr-Edwards ball valve in 1965-70 while  
74 had disc valve implantation either Bjork-Shiley or  
Lillehei-Kaster valve in 1971-75 As shown in Table I  
most of the patients were between 65 and 70 years only  
a few more than 70 years old The oldest patient was 73  
years

The follow up was completed by Jan 1 1977 with an  
observation period ranging from 1 to 11 years The fate of  
the patients has been studied by questionnaire to the pa-  
tients doctors The actuarial method (4) has been used to  
analyze the survival in these patients Those who had  
been operated on during 1965-75 have been analyzed  
separately for each year These groups have then been  
lumped together to calculate the cumulative proportion of  
surviving patients In this way we get a survival curve  
from year to year These survival curves have been com-  
pared to the survival curve for the Norwegian population  
according to mortality statistics from the years 1973-74  
matched for sex and age

## RESULTS

Fig 1 shows the survival curve for patients with  
aortic ball valve implantation aged more than 65  
years at operation This curve is compared to the  
corresponding survival curve for patients less than  
65 years old and the survival curve for the Nor-  
wegian population with the same sex and age dis-  
tribution Elderly patients have been followed for  
up to 11 years the younger for only up to 5 years  
Both groups of ball valve implantation show a mor-  
tality of 20-25% during the first year Later the

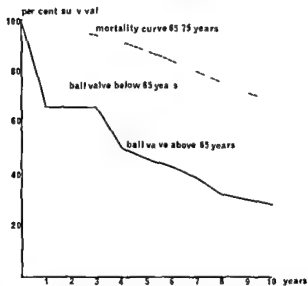


Fig 1 Survival curve for patients with aortic ball valve replacement below and above 65 years compared to the mortality curve for the Norwegian population of corresponding age

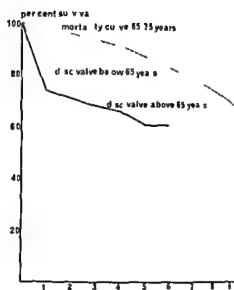


Fig 2 Survival curve for patients with disc valve implantation below and above 65 years compared to the curve for the Norwegian population of corresponding age

curve for the younger patients flattens out while elderly patients show a rather rapid fall from the third year on. After 10 years only 30% of the elderly patients are alive.

Fig 2 shows the corresponding curves for patients who had disc valve implantation. The observation period for the elderly patients is up to 6 years and for the younger up to 4 years. A considerable difference in survival between younger and elderly patients is evident. After 4 years the difference is only 6%.

## DISCUSSION

Only a few studies have been made previously on the fate of elderly patients operated on with aortic valve replacement. In 1969 Ahmad and Starr (2) studied 63 patients more than 60 years of age who had a Starr-Edwards prosthesis implanted in the aortic ostium. The operative mortality in this group was 19% and the late mortality 9%. These percentages are within the same range as those of patients in the younger age group. The oldest patient in their series was 75 years old and he was doing well 3 years after aortic valve replacement. Ahmad and Starr in their above mentioned study recommended that age should not be a contraindication to valve replacement. Acar et al (1) reported on 33 patients who had aortic valve replacement after 60 years of

age. The operative mortality was 16% in individuals more than 60 years of age, 7% to 18% in individuals below that age. The mortality was mainly due to the greater prevalence of coronary artery disease in the older age group. Oh et al (9) studied 73 patients who had aortic valve replacement after 60 years of age. The operative mortality was 15% and late mortality 10%. There was a functional improvement in 77% of the surviving patients and the majority were able to work. The writers conclude that although the operative mortality was higher than in younger patients, elderly patients should be offered the same treatment in view of the serious prognosis for patients who are already severely incapacitated from aortic disease. Fishman et al (6) found the same operative mortality (15%) among 100 patients above 60 years of age subjected to valve replacement as among younger patients (14.3%). During the last 10 years the postoperative mortality had dropped to 5%. De Bono et al (3) studied 40 patients aged 60 years who had aortic valve replacement and 40 patients who had disc valve implantation. In 1973 76% of these patients died in the postoperative period and none in the follow-up period of 13 years.

This study shows that aortic valve replacement in patients more than 65 years of age can be carried out with a tolerable risk. The operative mortality is considerably greater than for younger patients.

## Age distribution at operation

N

20  
19  
13  
24  
13  
3  
3  
2  
1  
98

Table II Causes of death among patients in the present and a previous study (11)

	Early	Late	Total
<i>Present study (n=98)</i>			
Heart failure	6	13	19
Arrhythmias	5	0	5
Infection	3	0	3
Myocardial infarction	3	2	5
On the table	3	-	3
Embolism	0	3	3
Carcinoma	0	2	2
Total	20	20	40
<i>Previous study (n=243)</i>			
Arrhythmia	12	0	12
Myocardial failure	14	3	17
Sepsis infection	6	6	12
Myocardial infarction	8	1	9
Embolism	1	4	5
Aortic rupture	0	1	1
Unknown	0	4	4
Carcinoma	0	1	1
Total	41	20	61

rm follow up shows that among patients who c valve implantation the survival is almost as or elderly as for younger patients while the ty increased rapidly from the third year on patients with ball valve implantation. The for a better prognosis in disc valve than in lve implantation is not clear. The difference due to the fact that the patients had been ed on in different periods because the im l survival after disc valve implantation also to patients in the younger age group. It may due to better hemodynamic performance by alve than by ball valve prosthesis. It is rthy that Starr and Lawson (10) presented a al curve from 1972-74 for 221 patients over 60 with isolated aortic ball valve replacement is almost identical to our curve presented in

le II shows that the causes of death among patients both for hospital and late mortality at much different from what we have found g younger patients in an earlier study (11). The causes of hospital mortality in both series myocardial failure, arrhythmia and infection deaths are predominantly due to myocardial

One should perhaps have expected a higher lity from myocardial infarction for elderly for younger patients but there is as we see stinct difference between the two series and vely few died from myocardial infarction. As ll known changes in the coronary arteries ase with increasing age. These changes have studied in patients with aortic stenosis by ock (7). He found by coronary angiography cant stenosis in one or more coronary arteries % of 133 patients under 40 years with aortic sis in 60% of those aged 40-60 years and in

68% of those older than 60 years. Coronary arterial stenoses were found more frequently among pa tients with angina pectoris namely in two-thirds but even among patients without angina pectoris significant stenosis of one or more coronary arteries were found in one third. In a previous study of 100 patients with aortic valvular disease significant coronary artery stenosis was found in 25% mainly in the age group 60-69 years (12). In these older patients there are also other causes of death pre dominantly carcinoma. Two deaths due to cancer occurred in the present series during the follow up period.

## CONCLUSION

This study shows that patients more than 65 years of age may be operated on for aortic valve disease with valve implantation on the same indications as younger patients. With the disc valves which are used today the elderly patients do not run any sig nificantly higher risk of operative or late mortality than the younger.

## REFERENCES

1. Acar J, Laborde J P, Azancot I, Pouget P & Garmierman J. La chirurgie officielle aortique au dela de 60 ans. Arch Mal Coeur 66: 975 1973.

- 2 Ahmad A & Starr A Valve replacement in geriatric patients *Br Heart J* 31 322 1969
- 3 De Bono A H B English T A H & Milstein B B Heart valve replacement in the elderly *Br Med J* 2 917 1978
- 4 Cutler S J & Ederer F Maximum utilization of the life table method in analyzing survival *J Chron Dis* 8 699 1958
- 5 Davies L G Valve replacement *Br Heart J* 32 723 1970
- 6 Fishman N H Roe B B Ebert P A & Hutchinson J C Results of cardiac valve replacement in elderly patients during a 10 year period *Abstr Congr Eur Soc Cardiovasc Surg* 41 1977
- 7 Hancock E W Aortic stenosis angina pectoris and coronary artery disease *Am Heart J* 93 382 1977
- 8 Morgans C M Barritt D W Belsey R H Keen G & Wensley R Late results of aortic placement with the Starr Edwards prosthesis *Heart J* 32 812 1970
- 9 Oh W Hickman R Emanuel R M Dr Somerville J Ross D Ross K & Gonzalez L Heart valve surgery in 114 patients over 60 *Br Heart J* 35 174 1973
- 10 Starr A D & Lawson R Cardiac surgery in the elderly In *Cardiology in old age* (ed F J J L C Dall & R D Kennedy) p 362 Press New York and London 1976
- 11 Storstein O & Efskind L Immediate results of aortic ball valve replacement *Scand Cardiovasc Surg* 6 114 1972
- 12 Storstein O & Enge I Angina pectoris in valvular disease and its relation to coronary artery disease *Acta Med Scand* 205 275 1979

# Prediction of Survival in Patients with Acute Myocardial Infarction

*A Clinical Study on 100 Consecutive Patients*

G Björck, L R Erhardt and G Lindberg

*From the Department of Medicine Serafimerlasarettet Stockholm Sweden*

**ACT** Expected survival after acute myocardial infarction (AMI) in 100 consecutive patients was judged by three doctors and two nurses at the time of discharge from a CCU. Predictions were compared with various coronary prognostic indices (CPI) and found to be too optimistic for the first 9 months. Senior physicians made more reliable predictions than junior physicians and nurses. All patients with a predicted survival of more than 10 years survived after 1 year and all with predicted death within one month died during the first year. Interphysician predictions were unreliable with reference to 1-year survival. Regardless of which CPI was used, a low index score carried a very low one-year survival and a high index a high mortality. Interphysician index scores were unreliable. A comparison of the predictions and index scores showed that as no difference in sensitivity and specificity between the methods. Our study thus shows that patients with either a very good or a very poor prognosis will be identified regardless of the method used. The problem of identifying the individual with an adequate risk remains to be solved.

*Index words:* acute myocardial infarction, prognostication, prognostic index, subjective estimate, receiver operating curve.

Acta Med Scand 206 165 1979

Accurate prognostic judgement would greatly help patients, families and physicians in the management of patients with acute myocardial infarction (AMI). Various coronary prognostic indices (CPI) have been used to predict survival in patients with AMI (1-6). However, these CPIs only indicate the relative likelihood of being dead or alive after a certain period. They have not permitted a prognosis as to expected survival in an individual patient. The primary purpose of our study was to investigate whether members of a coronary care unit (CCU) staff, guided only by their clinical impres-

sion of the patient and results of routine laboratory tests, could estimate the survival time for patients with AMI. Secondly, we aimed at comparing the results of these estimates with those of three CPIs. The predictions and outcome were evaluated after one year.

## PATIENTS AND METHODS

The study group consisted of 100 consecutive patients with AMI treated in the CCU at Serafimerlasarettet, Stockholm, between Aug. 1975 and May 1976. Six patients suffered re-infarctions and were seen twice. There were 68 men (mean age 67.2 years, range 31-82) and 32 women (mean age 70.1 years, range 56-85).

At the time of discharge from the CCU, usually after 48 hours' treatment, three doctors (the head of the CCU, a junior and a senior resident) and two nurses (the head nurse and a research assistant) predicted each patient's probable length of survival according to seven categories: 1) More than 10 years, 2) 5-10 years, 3) 1-5 years, 4) 3-12 months, 5) 1-3 months, 6) 1-4 weeks, 7) less than one week. All variables needed to calculate the three CPIs were collected continuously without the knowledge of the staff. The most complex index, as presented by Peel et al (6), includes seven parameters (sex, age, previous history, shock, heart failure, ECG and heart rhythm). The long-term CPI of Norris et al (5) is based on age, previous history, heart failure and heart size. The long-term CPI presented by Helmers (1) utilizes only two variables—age and respiratory rate on admission to the CCU.

During the study period, 492 individual predictions were performed and a mean predictive value was calculated for each patient. In order to compare the prognostic ability between different members of the staff, we applied a method derived from information theory (4). The individual estimates of expected survival and the various in-

**Abbreviations:** AMI = acute myocardial infarction, CPI = coronary prognostic index, CCU = coronary care unit, ROC = receiver operating curve, TP = true positive, FP = false positive.

Requests for reprints to: L R Erhardt, Medical Department Serafimerlasarettet, S-11227 Stockholm, Sweden.



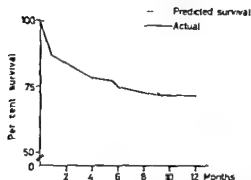


Fig 1 Mean actual and subjectively predicted cumulative one year survival in 100 AMI patients

dex scores supposedly carry some information about the patient's prognosis. With respect to one year survival all individual predictions were categorized as true or false positives or true or false negatives. True positives were predictions of death within one year (categories 4-7) which matched with death. False positives were predictions of death in patients who survived. Such categorization made it possible to calculate the information content of subjective estimates of different observers. The information content was calculated as the average reduction of uncertainty using the formula of Nishiyama et al (4).

The receiver operating curve (ROC) technically described by Metz et al (3) was used to compare the prognostic value of subjective estimates with the value of index scores. When using index scores to predict the prognosis of individual patients a cut-off point along the score range must be chosen. An index score above this point will forecast a poor prognosis (death within one year) while scores below the cut-off point will indicate a good prognosis (survival more than one year). If a very low index score is chosen as the cut-off point a large number of patients with a favourable prognosis will receive the same prediction and vice versa, corresponding to a change in the relation between sensitivity and specificity. The proportion of accurately predicted patients with poor prognosis is called the TP ratio. The false positive (FP) ratio is the proportion of patients with good prognosis falsely predicted to have a poor prognosis. The ROC curve monitors the changes in these ratios when the cut-off point is moved along the index score range. The ROC curve for the subjective estimates was constructed from cut-off points for the seven classes of the length of probable survival.

## RESULTS

During the first year 29 patients died (28 of myocardial infarction and one of aortic aneurysm). Fig 1 shows the survival curves derived from the mean predicted values and from actual events. Predictions of short term prognosis were too optimistic for the first 9 months. A comparison with the actual survival after one year revealed that none of the

patients predicted to survive more than 9 months had died (Fig 2). At the other end of the scale all patients predicted to survive 3 weeks had died within one year. Obviously the prediction adequately identifies a very good or very poor prognosis. In addition, the prediction of the short term prognosis between 12 months was very unreliable (Fig 2). The chance of being alive after one year was approximately 50%.

The same tables were constructed for 6 year survival in relation to the index score and three CPIs (Fig 3). Like subjective predictions, index scores were valuable for identifying very good or very poor prognosis. Intermediate index scores were very unreliable regarding one year survival.

Table I shows the average reduction of uncertainty about one year survival that was provided by predictions of different members of the staff. The reduction of uncertainty when all predictions included was 0.860. As can be seen a senior physician put forward the most reliable predictions, reducing the average uncertainty by 0.272. On the other hand, the physician's predictions were only slightly more plausible than those expected from the coin, his average reduction of uncertainty being only 0.005. When the subjective estimates were grouped by staff categories the senior physicians

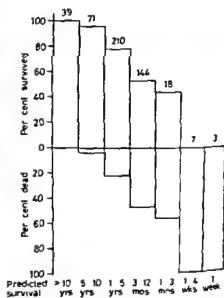


Fig 2 Actual survival after one year compared with subjective predictions. Figures above the bars indicate number of predictions made in each category.

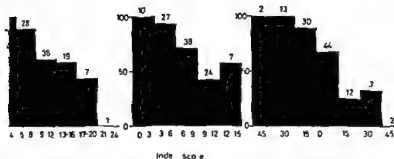


Fig 3 Actual survival after one year compared with the index scores of CPIs of Peel et al (6) Norms et al (5) and Helmert (1)

ed the highest information content in their tions (0.207) followed by their junior colleagues (0.082) and the nurses (0.044).

4 shows the ROC curve for the subjective estimates as well as for the three CPIs. The end of the curve for subjective predictions are all from hypothetical cut-off points where all of the estimates respectively are considered to forecast a poor prognosis, i.e. death within one year. There was no difference between the curve derived from index scores and the curve for subjective estimates. On the contrary they seemed to follow a common curve. This means that the same sensitivity and specificity was found regardless of the method.

## DISCUSSION

The study thus shows that clinical judgement and the use of CPI scores are equally good or bad for predicting the one year survival of patients after an AMI. As might be expected, the individual predictions were too optimistic with regard to short term prognosis. Obviously psychological mechanisms are involved, and it is probably only natural to

reject a prognosis of imminent death regardless of which disease is involved.

The similarity between individual prediction of prognosis and the CPI scores deserves some comment. Since the CPI score does not predict the time of death but rather indicates the relative risk of being dead after a certain interval, it may not be correct to compare it with individual predictions. It was assumed that in respect of one year survival the individual predictions worked as an ordinate discrete variable reflecting the probability of survival. An estimated survival of more than 10 years was supposed to bring a higher probability of living longer than one year than would an estimated survival of 3–12 months. This assumption made it possible to apply the ROC curve technique.

When comparing the prognostic results of individual predictions and CPIs, two further points should be considered. The first is that the ROC curve describes the changes of error rates as the cut off point is moved along the test scale or, as in this case, the index score. Although the ROC curve

Table 1 Average reduction of uncertainty regarding one year survival provided by the subjective predictions of different members of the CCU staff

CCU staff member	Average reduction of uncertainty (bits)
Senior physician	0.272
Nurse	0.165
Junior physician	0.151
Senior physician	0.134
Junior physician	0.118
Nurse	0.095
Junior physician	0.065
Nurse	0.016
Junior physician	0.005
Total	
Senior physicians	0.207
Junior physicians	0.082
Nurses	0.044

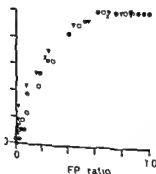


Fig 4 ROC curve showing cut-off points from subjective predictions (x), the CPIs of Peel et al (O) Norms et al (●) and Helmert (V).

does make it possible to compare error rates over the whole scale it still provides only a comparison between error rates. As pointed out by Shapiro (7) an error rate comparison does not take into account the magnitude of an error. Furthermore a false negative and a false positive prediction might not be of the same value or utility. The utilities can however be crucial for the choice of the cut-off point (7).

Knowledge of CPIs among the participants especially that of Helmers (1) may be one explanation for the similarity found between individual predictions and CPIs. There was however no difference in this respect between the doctors who were familiar with these indices and the nurses who were not. Furthermore no mutual influence among the participants was possible since all predictions were performed individually. The best predictions were made by a senior physician and a head nurse the latter with several years experience in the CCU. Whether this ability to prognosticate was due to a greater familiarity with the CPIs or to clinical experience is difficult to decide.

To conclude our study has shown that regardless of the method used patients with very good or very poor prognosis can be adequately identified. The problem of identifying patients with an intermediate risk remains to be solved.

## ACKNOWLEDGEMENT

This study was supported by a grant from the National Association against Heart and Chest Diseases.

## REFERENCES

- 1 Helmers C. Short and long term prognosis in acute myocardial infarction. *Acta Med Scand* (Suppl) 555 1974.
- 2 McNeil B J, Keeler E & Adelstein S J. Certain elements of medical decision making. *Med Decis Making* 293 211 1975.
- 3 Metz C E, Goodenough D J & Rosen. Evaluation of receiver operating characteristic data in terms of information theory with application to radiography. *Radiology* 109 297 1973.
- 4 Nishiyama H, Lewis J T, Ashare A B & E L. Interpretation of radionuclide imaging. Do training and experience make a difference? *Med Decis Making* 16 11 1975.
- 5 Norris R H, Caughey D E, Deming Mercer C J & Scott P J. Coronary flow index for predicting survival after recovery from myocardial infarction. *Lancet* 2 485 1970.
- 6 Peel A A F, Semple T, Wang I, Lancaster & Dall J L G. A coronary prognosis grading the severity of infarction. *Br Heart J* 1967.
- 7 Shapiro A R. The evaluation of clinical prognosis. A method and initial application. *Am J Med* 296 1509 1977.

# Early Mobilization and Discharge of Patients with Acute Myocardial Infarction

*A Prospective Study Using Risk Indicators and Early Exercise Tests*

K. Lindvall, L. R. Erhardt, T. Lundman, N. Rehnqvist and A. Sjogren

*From the Department of Internal Medicine, Serafmerla and St. Sockholm, Sweden*

**ABSTRACT.** Consecutive patients ( $n = 184$ ) surviving the first 24 hours in a coronary care unit were divided into a rapidly mobilized (RM) ( $n = 55, 30\%$ ) and one conventionally mobilized (CM) group ( $n = 129, 70\%$ ). The selection of RM patients was based on the absence of clinical risk indicators (RI) reflecting electrical changes and/or heart dysfunction. During after-care, RIs were evaluated, including a submaximal exercise test to 50 W, which excluded nine additional patients from the RM group. After excluding four patients for non-cardiac reasons, the remaining 42 RM patients were rapidly mobilized and discharged after a mean of nine days, in contrast to a mean of 19 days in the CM group, comprising 129 patients. No RM patient died in hospital and only one died during a six-month follow-up, compared to 17 ( $p < 0.01$ ) and 28 ( $p < 0.01$ ) patients respectively in the CM group. Both reinfarction and mortality increased with the number of positive RIs. A submaximal exercise test excluded four patients from the RM group. Altogether 22 of 45 patients showed abnormal ECG during exercise. Half of these 22 were readmitted due to cardiac complications during the follow-up period. These findings indicate that it is possible to identify a group of patients with AMI suitable for early discharge and that an early exercise test in selected good-risk patients is safe and identifies a group prone to complications during the early follow-up period.

**Keywords:** acute myocardial infarction, early mobilization, exercise tests, risk indicators.  
*Acta Med Scand* 206: 169-179, 1979.

The optimal duration of hospitalization in patients with acute myocardial infarction (AMI) is not known. Six weeks in hospital was proposed in 1955 by Loebe (5), who based their recommendation on the histologic study by Mallory et al. (7),

showing that it took some six weeks for an infarct to heal. Since then, hospitalization time has gradually decreased (9, 20, 30) and nowadays 14-21 days are commonly recommended (7).

Levine and Lown (18) introduced early armchair treatment after a non-complicated AMI and Prinzmetal et al. (28) advocated that patients with mild myocardial infarction should be activated early. Several subsequent reports have shown that both early mobilization and early discharge are possible in selected patients (1, 12, 13, 24, 35, 36). Boyle et al. (4) and Chaturvedi et al. (6) selected 67 and 40, respectively, of the 100 patients for early discharge by using risk indicators (RI) based on information from the first seven days of the illness. McNeer et al. (24) discharged after one week patients who had been without complications during the first four days. No adverse effects from early mobilization and discharge in selected low-risk patients were reported in any of these studies.

The best way to select patients for rapid mobilization and early discharge is probably to assess the patients continuously during their hospital stay. The aim of this investigation was: 1) To evaluate the possibility of selecting patients for rapid mobilization (RM) and early discharge using RIs both after 48 hours of treatment in the Coronary Care Unit (CCU) and continuously during mobilization; 2) To follow all patients for six months in order to evaluate the mobilization schemes and RIs used; 3) To evaluate the information from an exercise test performed before discharge in RM patients.

**Abbreviations:** AMI, acute myocardial infarction; RI, risk indicator; CCU, coronary care unit; RM, rapidly mobilized; rapid mobilization; CM, conventionally mobilized; conventional mobilization; LD, lactate dehydrogenase; CK, creatine phosphokinase.

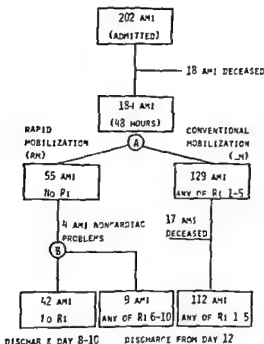


Fig 1 Schedule for admission, mobilization and discharge of 202 AMI patients. A=evaluation of early RIs after 48 hours' treatment in the CCU. B=evaluation of late RIs on days 3-8.

## METHODS

Criteria for admission, diagnostic and therapeutic routines in the CCU and after-care unit have been given elsewhere (14).

We chose to evaluate electrical and mechanical dysfunctions of the heart after 48 hours' treatment in the CCU by five RIs (early RIs). Patients without any RI at 48 hours formed the RM group and the remainder the conventional mobilized (CM) group. Enzyme values were determined twice a week in the after-care unit and 12 lead ECGs were recorded on days 3, 5 and 7. No long term ECG monitoring was performed. RM patients were transferred to the CM group if any one of five additional RIs was present during the mobilization (late RIs).

**Five early RIs** 1) A heart rate above 100/min or 2) a respiratory rate above 27/min for more than three hours were considered the two RIs indicative of left heart dysfunction. 3) Maximum enzyme values, either  $>36 \mu\text{kat/l}$  for heat stable lactate dehydrogenase (LD) or  $>18 \mu\text{kat/l}$  for creatine phosphokinase (CK), indicated a large infarct. 4) Treated supraventricular and ventricular arrhythmias were considered to be RIs reflecting electrical instability. Our treatment schedule in this respect is conventional, but frequent monofocal, multifocal or R-on-T ventricular ectopic beats were not treated unless they recurred within one hour. 5) Complete bundle branch blocks, AV block II and III developing in the CCU also excluded a patient from the RM group.

**Five late RIs** The RM group was continuously evaluated during mobilization and if one of the following RIs

was present, the patient was transferred to the CM group. 6) Signs or symptoms indicating reinfarction. 7) Arrhythmias requiring treatment. 8) A systolic time interval index (STI)  $>0.45$  or 9) a chest X-ray revealing pulmonary congestion. 10) A bicycle exercise test to a work load of 150 W performed on the 7th day. Two or more of the following findings during or after exercise excluded the patient from the RM group: heart rate exceeding 155 beats/min, ST segment elevation or depression  $>1 \text{ mm}$ , or arrhythmias requiring treatment and angina pectoris.

**Mobilization and discharge** All patients were under guidance of a physiotherapist. RM patients were allowed to sit from the third day onwards, to walk the ward from the fourth and were discharged on the 8th-10th day. In contrast, the CM patients were bedridden for 4-5 days, whereafter they were allowed to walk around the ward from day 7 onwards. Walking around the ward was allowed from day 9 onwards. The RM patients were seen as outpatients one week after discharge, when a new exercise test was performed and systolic time intervals were evaluated. Patients were thereafter seen six weeks and three months after discharge in the Out Patient Department.

**Statistics** Conventional statistical methods were used. Differences between relative numbers were tested by  $\chi^2$  test. Yates's correction was applied.

## PATIENTS

During the one year study period, 453 patients were admitted. Myocardial infarction was diagnosed in 202 patients, 184 of whom survived the first 48 hours. Fifty-five patients were free from RIs during the first 48 hours, thus forming the RM group, while 129 formed the CM group. The age and sex distributions were similar in both groups, with a mean age of 65 years, male:female ratio of 2:1. Nine RM patients were subsequently transferred to the CM group because of non-cardiac disorders, leaving 42 patients for discharge. Of these 42 patients, 39 could be followed within 10 days (mean 9). The corresponding for CM patients was 19 days (range 12-36).

## RESULTS

### Early risk indicators and mortality

The six month mortality in relation to the presence of positive early RIs is given in Table 1. A mortality (5%) was found in patients with one or more early RIs in the CM group against 39% in the RM group. No RM patient died on the first 48 hours, in contrast to 17 in the CM group ( $p < 0.001$ ). Of these 17 patients, 10 died in the CCU of cardiac failure, ten patients died during after-care, four of cardiac rupture, four of cardiac failure and one during sleep. One patient in the RM

<sup>a</sup> Mortality, reinfarction and readmission for other reasons than AMI and recovery during six months in relation to early and late RIs in RM and CM patients

within parentheses indicate per cent

Early RIs	RM patients (n=42)	CM patients (n=138)				Any late RIs
	0	1	2	3	4-5	
Died within 6 months	1 (2)	2 (5)	10 (21)	9 (35)	7 (39)	1 (11)
Readmission within 6 months	1 (2)	4 (11)	7 (15)	8 (31)	7 (39)	2 (22)
Readmission due to other IHD	6 (14)	8 (21)	18 (38)	8 (31)	3 (17)	5 (56)
Recovery	34 (81)	24 (63)	12 (26)	1 (4)	1 (6)	1 (11)
	42	38	47	26	18	9

patients in the CM group died of reinfarction by 21. The difference in total mortality on days 180 between the two groups is significant ( $p < 0.01$ ).

Mortality in relation to each RI is illustrated in Figure 2. The early RIs were associated with some different mortality patterns. RIs 2 and 5 were seen in 22 and 17% of the patients, respectively. RIs 1, 3 and 4 were seen in 33, 34 and 44% of the patients. Patients with RIs 2 and 5 showed a high early (days 2-21) mortality of 29 and 28% compared with 17 and 12% for RIs 1, 3 and 4, respectively ( $p < 0.01$ ).

The mortality in CM patients with only one early RI was comparable to that in the RM group. Patients were studied separately (Table II). A poor prognosis was noted for the five patients with high enzymes, only though definite conclusions cannot be drawn because of the small number of patients.

#### Classification of late RIs

Initially 55 RM patients, five had been transferred to the CM group due to the presence of late RIs. The exercise test and another four were excluded because of non cardiac problems. Accordingly 46 patients performed the exercise test on day 21. Of these 46 patients, 22 developed one or more late RIs. Two of the pathological parameters during the exercise test (Table III) thus excluding 24 patients from early discharge. Three of four patients were later readmitted because of chest pain and reinfarction developed in one. When analyzing the 26 patients with abnormal findings at day 21 (Table II), one of seven with a heart rate exceeding 125/min died within six months, three were reinfarcted and three were readmitted for other

IHD manifestations. Of the 6 patients with angina at exercise, three reinfarcted and two were readmitted for other IHD manifestations.

#### Reinfarction and readmission

None of the RM patients had developed signs or symptoms suggesting any cardiac complications when examined one week after discharge. Two per cent of the RM patients reinfarcted within six months against 20% of the CM patients ( $p < 0.01$ ). The frequency of reinfarction increased from 11% in patients with one early RI to 39% in patients with four or five RIs (Table I). Two of the nine patients transferred from the RM to the CM group developed a new infarct.

Six (14%) of the RM patients were readmitted for other reasons than AMI (angina pectoris, arrhythmias, congestive heart failure, etc.) (Table I). In patients with one or more early RIs the corresponding figures were 17-38%. Five (56%) of the nine patients with late RIs were readmitted during the six month follow up.

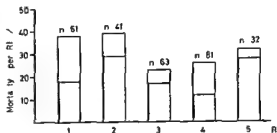


Fig. 2 Mortality for each early RI in 184 AMI patients between days 2 and 21 (■) and between days 22 and 180 (□).

Table II Mortality and IHD morbidity in 47 patients with one RI only during the six month follow-up. For RI 1-10 see text

	RI 1	RI 2	RI 3	RI 4	RI 5	Any RI 6
Diseased	1	-	-	1	-	1
Reinfarction	1	1	-	1	1	2
Readmission for other IHD	2	2	-	2	2	5
Normal recovery	6	2	5	11	-	14
Total	10	5	5	15	3	38

### Recovery and return to work

Of the RM patients 81% had a normal recovery compared to 29% of the CM patients (Table I). The RM patients were more often in active work prior to their AMI (69%) than CM patients (47%). RM patients resumed work both earlier and more frequently than CM patients (Fig. 3). Thus, among those working before the AMI 24% ( $n=7$ ) of the RM patients and 5% of the CM patients had returned to work at three months. The corresponding figures after six months were 66 and 25%.

## DISCUSSION

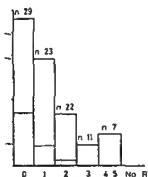
Most complications in AMI occur during the first 48 hours (15). They are, however, still frequent 2-3 weeks after an AMI (24-34), a fact that probably has prevented trials of rapid mobilization and early discharge (25). On the other hand, immobilization has well known disadvantages, e.g. thrombotic episodes (22-27), muscle wasting and orthostatic intolerance (8). Rapid mobilization has not been found to increase the incidence of complications such as aneurysm formation or rupture in selected groups of AMI patients (11-12). Short periods of immobilization would therefore seem pref-

erable in selected patients with a low risk of complications (13). Several studies have been performed regarding the feasibility of early mobilization and discharge in selected patients. Most of these have been uncontrolled (4, 24, 28, 37), but a few controlled studies have appeared (6, 16). None of these investigations showed adverse effects of early mobilization and discharge, and seemed feasible and ethically justified to enter into a prospective clinical trial of early mobilization and early discharge in patients with uncomplicated AMI. No previous studies have been found combining early selection of candidates for mobilization and early discharge.

In order to select low risk patients we used several indicators both after 48 hours treatment and continuously during mobilization. The RIs were used to exclude patients with severe mechanical or electrical dysfunction of the heart from mobilization. A heart rate above 100/min and a respiratory rate above 27/min have previously been considered good predictors for early as well as late mortality (4, 13, 14, 16, 24, 36). CK and the percentage fraction of LD correspond fairly well with the extent of the myocardial necrosis (3, 7, 33). Our use of CK and LD<sub>1</sub> were based on the studies of Sjö-

Table III Findings during exercise test on the seventh day after AMI in relation to mortality, re-hospital treatment and recovery in 46 patients

	Angina pectoris	Heart rate >125/min	ST deviation >1 mm	Arrhythmia
Mortality (days 22-180)	-	1	1	-
Reinfarction (days 22-180)	3	3	1	-
Hospital treatment for other IHD manifestation	2	3	3	1
Normal recovery	1	-	7	-
Total	6	7	12	1



Patients resuming work within three (□) and six (■) weeks after AMI. n=Number of patients in active work prior to discharge from hospital. No RI=number of patients with no reinfarction.

hardt (7) with the intention of excluding patients within the upper third of the enzyme scale who had high enzyme levels as their only criterion. However, it proved to have a relatively low morbidity. Obviously major structural damage does not only lead to abnormal heart function and/or increased risk of complications. Severe ventricular arrhythmias in the early phase of an AMI have been found to be related to severe myocardial damage in large infarcts but also to be an independent predictor of future complications (26-29, 31). Supraventricular arrhythmias are related both to age and to the presence of heart failure and may therefore also be related to an increased risk. Patients with intraventricular as well as AV nodal conduction disturbances also have a high incidence of complications and a raised mortality during the early convalescence period (16-24). We made this clear in 32 of our patients and mortality during the first three weeks was approximately 30%. This is in agreement with previous findings (19). The use of RIs in the evaluation of patients for early mobilization schemes has been different. Patients without RIs in our study had a very low incidence of reinfarction during the follow up period and only one patient died. Similarly few complications were seen in patients with only one RI indicating that RM could be extended also to these patients. Hayes et al (13) mobilized their patients according to an index score after 48 hours treatment but the patients remained in hospital for 10-14 days. In contrast Boyle et al (14) and Chaturvedi et al (6) used RIs based on all information

available after the first six or seven days with the purpose of selecting patients to be discharged from day eight onwards.

Applying a mobilization program as used in our study some 25% of the AMI patients may safely be discharged after 8-10 days. This figure is low compared to 40-60% presented in other studies (4, 6, 24). On the other hand another 20% i.e. patients with one RI only had the same outcome but with CM. The final decision about discharge in the RM group was made after an exercise test. Exercise tests have previously been performed 2-3 weeks after an AMI (10, 17) without apparent negative effects. The 50 W work load resulted in a mean increase in heart rate from 72 to 103/min which is in agreement with the results of Ibsen et al (17) at the corresponding work loads in patients exercising three weeks after an AMI. Excessive heart rates and angina pectoris during the test appeared to be sensitive parameters for later complications. A light exercise corresponding to stair walking may also have reduced anxiety.

The time of return to work is often used as a parameter to measure the success of rehabilitation schemes following AMI. Several factors however will affect the time of resuming work and Winter and Kellerman (39) suggested that the socio-economic structure of different countries including the degree of unemployment is the basic determining factor. Accordingly figures in unselected patient groups vary between 17 and 90% (38, 39) six months post AMI which may be compared to 66 and 25% in the RM and CM groups in our study. As the male/female ratio and mean age were similar in the RM and CM groups the difference probably reflects a higher pre AMI morbidity in the CM than in the RM group which in turn may increase the probability of developing complications. As no control group is available in our study little may be concluded about a possible shortening of convalescence in the RM group. Also we know little about the benefit—if any—of keeping the remaining patients i.e. those with RIs in hospital for longer periods.

There are obvious economic benefits associated with early discharge of AMI patients (23). Our study indicates that 7-10 days of high-cost care could be saved for each RM patient which corresponds to total saving of some 400 hospital days/year in our hospital. Possibly in the future low risk patients may spend an even shorter time in hospital and be



more rapidly mobilized than is the present routine. The mobilization and discharge decisions must however always be made individually in order to minimize any risk involved to the patient.

# ACKNOWLEDGEMENT

This study was supported by the Swedish National Association against Heart and Chest Diseases.

# REFERENCES

- 1 Adgey A A J. Prognosis after early discharge from hospital of patients with acute myocardial infarction. *Br Heart J* 31: 750 1969.
- 2 Ad Hoc Committee Review. Swan H J C, Blackburn H W, De Sanctis R, Frommer P L, Hurst J W, Paul O, Rapaport E, Wallace A & Weinberg S. Duration of hospitalization in uncomplicated completed acute myocardial infarction. *Am J Cardiol* 37: 413 1976.
- 3 Ambos H D, Roberts R, Oliver G C, Cox J R Jr & Sobel B E. Infarct size: A determinant of persistence of severe ventricular arrhythmias. *Am J Cardiol* 37: 116 1976.
- 4 Boyle D, McC, Barber J M, Walsh M J, Shivalingappa G & Chaturvedi N C. Early mobilization and discharge of patients with acute myocardial infarction. *Lancet* 2: 57 1972.
- 5 Cecil R L & Loeb R F. A textbook of medicine ed 4 p 1336 Saunders Philadelphia 1955.
- 6 Chaturvedi N C, Walsh M J, Evans A, Munro P, Boyle D, McC & Barber J M. Selection of patients for early discharge after acute myocardial infarction. *Br Heart J* 36: 533 1974.
- 7 Erhardt L R. Clinical and pathological observations in different types of acute myocardial infarction. *Acta Med Scand (Suppl)* 560 1974.
- 8 Fareeduddin K & Abelman W H. Impaired orthostatic tolerance after bed rest in patients with myocardial infarction. *N Engl J Med* 280: 345 1969.
- 9 Gilchrist A R. Problems in management of acute myocardial infarction. *Br Med J* 1: 215 1960.
- 10 Granath A, Södermark T, Winge T, Volpe V & Zetterqvist S. Early work load tests for evaluation of long term prognosis of acute myocardial infarction. *Br Heart J* 39: 758 1977.
- 11 Groden B M, Allison A & Shaw G B. Management of myocardial infarction. The effect of early mobilization. *Scott Med J* 12: 435 1967.
- 12 Harpur J E, Kellett R J, Conner W T, Galbraith H J B, Hamilton M, Murray J J, Swallow J H & Rose G A. Controlled trial of early mobilization and discharge from hospital in uncomplicated myocardial infarction. *Lancet* 2: 1331 1971.
- 13 Hayes M J, Morris G K & Hamptom J R. Comparison of mobilization after two and nine days in uncomplicated myocardial infarction. *Br Med J* 3: 10 1974.
- 14 Helmers C. Short and long term prognostic indices in acute myocardial infarction. *A clinical study. Med Scand (Suppl)* 555 1974.
- 15 Hofvendahl S. Influence of treatment in a care unit on prognosis in acute myocardial infarction. *A clinical study. Acta Med Scand (Suppl)* 555 1974.
- 16 Hutter A M Jr, Sidel V W, Shinn J, De Sanctis R W. Early hospital discharge after myocardial infarction. *N Engl J Med* 288: 1141 1973.
- 17 Ibsen H, Kjoller E, Styperek J & Pedersen J. Routine exercise ECG three weeks after myocardial infarction. *Acta Med Scand* 198: 46 1975.
- 18 Levine S A & Lown B. Armchair treatment of acute coronary thrombosis. *JAMA* 148: 141 1941.
- 19 Lichstein E, Letafati A, Gupta P K & K D. Continuous holter monitoring of premature beats complicating anterior wall myocardial infarction. *Am J Cardiol* 40: 860 1977.
- 20 Lown B & Sidel V W. Duration of bed rest following acute myocardial infarction. *Am J Cardiol* 23: 1 1969.
- 21 Mallory G K, White P D & Salcedo J. The speed of healing of myocardial infarction. *Heart J* 18: 647 1939.
- 22 Maurer B J, Wray R & Shillingford J. Prevention of venous thrombosis after myocardial infarction. *Lancet* 2: 1385 1971.
- 23 McNeer J F, Wagner G S, Ginsburg J, Wallace A G, McCants C B, Conley M J, R A. Hospital discharge one week after myocardial infarction. *N Engl J Med* 298: 23 1978.
- 24 McNeer J F, Wallace A G, Wagner G S, Conley M J, R A & Rosati R A. The course of myocardial infarction. Feasibility of early discharge of the uncomplicated patient. *Circulation* 50: 1975.
- 25 Miller A J. Rehabilitation and length of hospitalization after acute myocardial infarction. *Am J Cardiol* 32: 547 1976.
- 26 Moss A J, De Camilla J, Davies R, Lown B, Goldstein S. Use and limitations of premature beats as prognostic indicators of the hospital course of myocardial infarction. *Am J Cardiol* 37: 158 1976.
- 27 Murray T S, Cox F C, Lorimer A R, Lown B, Leggett R. Venous thrombosis following myocardial infarction. *Lancet* 2: 792 1970.
- 28 Prinzmetal M, Weiner S M & Bhargava R. Mild myocardial infarction. Clinical features and new method of management. *Am J Cardiol* 1958.
- 29 Rehnqvist N & Sjögren A. Ventricular fibrillation prior to discharge and one year after acute myocardial infarction. *Eur J Cardiol* 5/3: 425 1977.
- 30 Riedel D C & Fitzpatrick T B. Patterns of care pp 25 175. University of Michigan Press Ann Arbor 1964.
- 31 Ruberman W, Weinblatt E, Frank C W, Lown B J D. Characteristics of ventricular premature beats and prognosis of men with coronary disease. *Am J Cardiol* 37: 168 1976.
- 32 Sawe U. Early diagnosis of acute myocardial infarction with special reference to the diagnosis.

- mediate coronary syndrome. A clinical study. *Med Scand (Suppl)* 445: 1973
- 7 B E Roberts R & Ambos H D The effect of infarct size on ventricular dysrhythmia. *Med Scand (Suppl)* III: 110: 1974
- 8 L yza N Murphy M L Bissett J K Kane J & Joherty J E In hospital mortality after acute myocardial infarction. *South Med J* 68: 474: 1975
- 9 klen F H N Besterman E M M Everest J & Litchfield J W & Petrie M Late ventricular dysrhythmias after myocardial infarction. *Br Med J* 1: 1968
- 10 pson P & Sloman G Sudden death in hospital. Discharge from coronary care unit. *Br Med J* 1: 1971
- 37 Tucker H H Carson P H M Bass N M Sharrott G P & Stock J P P Results of early mobilization and discharge after myocardial infarction. *Br Med J* 1: 10: 1973
- 38 Wilhelmsson C E Hjärtinfarkt i Göteborg 1969-1970. Analys av fynd under sjukhusvistelse och efter förlopp. Göteborg 1974
- 39 Wintner J & Kellerman J J Psychological approach to the rehabilitation of coronary patients. In: International Society of Cardiology Scientific Council on Rehabilitation of Cardiac Patients. p. 158. Springer Verlag. Berlin Heidelberg and New York 1976



# Arrhythmias in the Coronary Care Unit Recognized with the Aid of Automated ECG Monitoring

A Twelve Month Study in 679 Patients

Johan Hulting

Department of Medicine I, Södersjukhuset, Stockholm, and the Department of Medical Informatics,  
Länköpings University, Länköping, Sweden

**ACT** Arrhythmia incidence in 339 patients  
1340 without proven acute myocardial in-  
(AMI) has been compared with the aid of an  
ed arrhythmia monitoring system. Seventeen  
s of arrhythmia could be made with the sys-  
resulted in alarms. All ECG write-outs were  
manually. The patients were further divided  
classes of previous myocardial infarction  
vious or present heart diseases (HD) and no  
HD. Except for atrial fibrillation or flutter  
dyscardia, all arrhythmias studied were sig-  
y more common in patients with than with  
I. Arrhythmia incidences in AMI/non AMI  
regarding paired ventricular ectopic beats  
tachycardia (heart rate >120/min) par-  
supraventricular tachycardia (SVT) and  
an 5 VBs per min were 72/38, 55/34, 50/22,  
29% respectively. Arrhythmia incidence in  
ous subclasses of AMI patients did not differ  
ly. In the non AMI group, most ventricular  
mas were less common in patients without  
mortality in asystole, ventricular fibrillation,  
tricular tachycardia (VT) did not differ be-  
AMI and non AMI patients. Most other ven-  
and supraventricular arrhythmias were as-  
with a poorer prognosis in AMI than in  
II patients. No statistical difference in out-  
as observed between AMI patients with and  
VT. In AMI, paired VBs or SVT carried a  
gnosis during stay in the Coronary Care  
CU). The prognostic implications of several  
as and possibly the indications for antiar-  
treatment in the CCU will be changed with  
monitoring methods.

Is acute myocardial infarction arrhythmias  
coronary care unit monitoring prognosis  
Scand 206 177 1979

years automated arrhythmia monitoring  
have gained widespread use in coronary  
s (CCUs). The majority of these systems

are commercial but despite several years of experi-  
ence with such systems very few clinical evalua-  
tions have been presented so far. An automated  
arrhythmia monitoring system has been developed  
in the CCU of Södersjukhuset, Stockholm. The per-  
formance of this system has been tested in long  
term routine monitoring (11-13). The monitoring  
system has been used in the present study to  
evaluate arrhythmia incidence in the CCU. The  
CCU and hospital mortalities in different ar-  
rhythmias were also estimated.

## PATIENTS

A total of 850 cardiac patients were admitted to the CCU  
for automated ECG monitoring during a 12 month period  
ending in April 1978. Excluded from the study were 157  
patients with unsuspected and non proven acute myocar-  
dial infarction (AMI) as well as 14 patients with an uncer-  
tain or a long (>96 h) admission delay defined as the time  
between onset of symptoms and start of monitoring. Thus  
the study comprised 669 admissions due to a suspected  
myocardial infarction (MI) and 10 patients with AMI ad-  
mitted for other reasons (mainly pulmonary oedema).

During the 12 month period an additional number of 86  
patients were admitted for ECG monitoring but observed  
in a general medical intensive care unit (ICU) located next  
to the CCU and run by the same personnel. Reasons for  
ICU admissions were 1) impending or manifest respira-  
tory failure, 2) unconsciousness following resuscitation  
and 3) all beds in the CCU occupied. Fourteen patients

**Abbreviations:** AF atrial fibrillation or flutter, AMI  
acute myocardial infarction, AV atrioventricular, CCU  
coronary care unit, ECG = electrocardiogram, elec-  
trocardiograph, HD heart disease, HR heart rate,  
ICU intensive care unit, MI myocardial infarction,  
RIR rapid idioventricular rhythm, S-ALAT serum  
alanine aminotransferase, S-ASAT serum aspartate  
aminotransferase, S-LD serum lactate dehydrogenase,  
SR sinus rhythm, SVB supraventricular ectopic beat,  
SVT paroxysmal supraventricular tachycardia, VB =  
ventricular ectopic beat, VF = ventricular fibrillation, VT  
ventricular tachycardia.

transferred from the ICU to the CCU were included in the results. Forty two AMI patients not included were treated in the ICU with a mortality of 57%.

#### Diagnostic groups

According to the final diagnosis the total patient material was divided into an AMI group ( $n=339$ ) and a non AMI group ( $n=340$ ). The groups were subdivided into the following classes: a) previous MI, b) previous or present heart disease (HD) without previous MI and c) no known HD prior to admission and as to the non AMI group HD unproven during CCU stay.

#### Diagnostic criteria

The criteria for diagnosis of AMI were subjective symptoms leading to the suspicion and the development of pathological Q waves or R wave progression or two or more elevated serum aspartate aminotransferase (S-ASAT) values with a maximum 1-2 days after onset of symptoms and higher than a simultaneous serum alanine aminotransferase (S-ALAT) value or myocardial necrosis at autopsy corresponding in age to the onset of symptoms. The isoenzymes of serum lactic dehydrogenase (S-LD) were measured on the first and second day after admission and used as a diagnostic complement in patients with a long admission delay in whom the transferase values may have returned to normal. A typical history of AMI with questionable S-LD and aminotransferase values together with unspecific ECG changes e.g. ST wave changes was diagnosed as angina pectoris. The diagnosis of previous MI was based on history, hospital records, ECG or autopsy. Angina pectoris was considered in patients with typical symptoms for at least one month prior to admission.

## METHODS

#### The automated monitoring system

Eight patients could be monitored simultaneously on the automated monitoring system. The system and the principles for arrhythmia analysis have been described in great details elsewhere (28).

A total of 17 arrhythmia alarms and 7 alarms regarding the configuration of the ECG signal (monitoring status alarms) were reported by the system. In the present study the definitions of arrhythmias in the computer program and in a subsequent manual interpretation were identical for most arrhythmias. The alarm multiform VBs was excluded from the study because of difficulties in verifying this alarm from the short ECG strip available for interpretation. The alarms were ranked and grouped into three priority levels. When a particular arrhythmia event fulfilled the criteria for more than one diagnosis the highest priority (ranking) condition was chosen by the computer. A 2-channel Mingograph was activated at arrhythmia alarms. One channel showed room number, time of the event and the computer diagnosis, the other a 5 sec. retroactive ECG (paper speed 10 mm/sec). Usually this write-out had a duration of 15 sec. All write-outs were collected and analysed off line by the author. This interpretation was made without any clinical information on the patients. However in some patients in whom the single-channel ECG did not allow an accurate diagnosis the hospital records were studied in retrospect.

#### Definition of arrhythmias

The principles of beat classification used here have been described earlier (11). Questionable beats were classified as supraventricular.

The diagnoses of arrhythmias were made with consideration of the diagnostic message given by computer except for the R-on-T phenomenon, bigeminy and frequent ventricular or supraventricular beats (VBs or SVBs). There was no algorithm for the recognition of atrial fibrillation (AF) and AV block II-III. All arrhythmias except two were ranked. A special alarm missing the sensitive to abrupt changes in heart rate (HR) in intermittent AV block II-III.

The following arrhythmias were studied: 1) R-R interval >5.0 sec. 2) Ventricular fibrillation: irregular oscillating rhythm with a duration >5 sec. 3) Absence of QRS complexes and atrial fibrillation: ventricular tachycardia (VT) four or more VBs with a rate of >120/min (VT<sub>120</sub>). 4) Short or three consecutive VBs with a rate of >100/min. 5) More than three VBs with a rate of 101-130/min. 6) Idioventricular rhythm (RIR) three or more VBs with a rate of 51-100/min. 7) Extreme bradycardia <35/min estimated over at least two consecutive intervals. 8) Paired VBs: two consecutive VBs with an interval of <1.2 sec. 9) Early VB: VB falling on the preceding ordinary beat. 10) Ventricular bigeminy or more VBs alternating with normal beats. 11) Paroxysmal supraventricular tachycardia (SVT) or more consecutive SVBs with a rate of >120/min. 12) Sinus rhythm documented prior to or after a bradycardia episode. 13) Frequent VBs: more than 5 VBs/min. 14) Frequent SVBs: more than 5 SVBs/min. 15) Tachycardia sinus or supraventricular rhythm: QRS rate of >120/min. 16) Bradycardia sinus or supraventricular rhythm with a QRS rate of <35/min. 17) Second or third degree AV block: absence of QRS complexes following a normal P wave. 18) AF: no P wave. 19) Irregular supraventricular rhythm with a length of 20-30 SVBs. A regular atrial flutter should be noted as a diagnostic ECG.

The highest ranked arrhythmia in each patient was noted. The delay between onset of monitoring and the first arrhythmia (arrhythmias 1-15) was estimated to 15 sec. to AF and AV block II-III only one diagnosis was noted from each write-out.

The HR in ordinary supraventricular and ventricular rhythm was obtained manually. If four consecutive VBs with a rate of >120/min occurred in a run of 15 sec. the episode was classified only as VT<sub>120</sub>. The average rate of the arrhythmia episode was calculated. The rate and length of all episodes of VT<sub>120</sub> were noted for each patient.

In the terminal phase only the first episode of VF or VT was noted. A run of VT (more than 3 complexes) passing into VF was documented as VF. Arrhythmias were not studied during or after resuscitation or during the implantation of a rare pacemaker. An ordinary pacemaker was ignored.

Uncertain interpretation concerning VT<sub>120</sub> and

d as the number of episodes regarded as ventricular premature beats in each patient. Thus for VT<sub>120</sub> three levels of diagnostic accuracy were used in final interpretation: 1) definite VT<sub>120</sub>, 2) probable VT<sub>120</sub> and 3) questionable VT<sub>120</sub>. 2) probable VT<sub>120</sub> referred to the VT category and 3) questionable VT<sub>120</sub> referred to the SVT category.

On T alarm was given by the computer system on VEBs with the same shape and a short coupling had been detected by the system within 15 min. If the limit of this coupling interval was corrected for the QT interval limit for a HR of 60/min was set to 0.15 s. Early VEBs were only studied when the correct alarm had been reported by the automated sys-

#### Uses of S-ASAT and S-ALAT in AMI

Maximum S-ASAT value sampled 18–48 h after the symptoms was used as a measure of the size of the AMI. Only an S-ASAT value at least 100% above a previous S-ALAT value was approved. The S-ASAT value begins to rise 8–10 h after the onset of the AMI and reaches a maximum after 20–30 h. It was used to estimate admission delay in a few patients more than one peak of chest pain prior to admission.

#### Arrhythmic treatment

Cardioversion was utilized in VF and life threatening bradycardia. Lignocaine was used as the drug of first choice in ventricular arrhythmia during the first 48 h after onset of the AMI and when a rapid effect was desired. Lignocaine was usually withheld until VT<sub>120</sub> or VF had been documented. It was administered according to a restrictive regimen: a bolus (75–100 mg i.v.) followed by a continuous infusion for at least 12 h at a rate of 1–3 mg/min. Oral amide quinidine and disopyramide were sometimes given against recurring ventricular arrhythmias but not in prophylaxis after VT or VF in the acute stage given routinely.

Digitalis was usually omitted on admission but diuretics were given liberally if signs of cardiac failure were present: rapid AF (HR>130) or in frequent SVT. Digoxin was usually tried first unless signs of heart failure were evident. In such cases digoxin was given. Digoxin was added to the regimen of patients with heart failure responding satisfactorily to several days of treatment with high doses of frusemide.

In symptomatic bradycardia atropine was first attempted. If this failed, total block, bradycardia and signs of low output were usually given an infusion of isoprenaline but if this regimen failed a transvenous pacing electrode was passed via the subclavian vein. No  $\beta$ -blocking agents before admission were given. If necessary this medication in the CCU unless contraindications were apparent.  $\beta$  blockers were given to patients with unstable angina pectoris but not routinely as antiarrhythmic agents.

Information regarding sex, age, admission delay, mean time in the CCU, previous treatment (digitalis,

diuretics,  $\beta$  blockers) and outcome was punched on cards together with data concerning diagnoses, arrhythmias, enzyme values etc. for further analysis with a general computer.

Student's *t* test and the  $\chi^2$  test (four field table, two-tailed test) with Yates' correction were used for the evaluation of statistical significances of means and relative numbers respectively at the 5% and 0.1% level. The exact test was used if the expected number in the four field table was 5 or less. All tests of significance were performed on a Texas Instruments calculator (SR 52). The term significant used below refers to a probability of  $p < 0.05$ .

## RESULTS

### General characteristics of the diagnostic groups (Table I)

The mean age in the AMI group was 66 years and 63 years in the non AMI group. AMI patients with HD were older and those without HD were younger than the rest. Non AMI patients without HD had a mean age more than 10 years below that of the others. The proportion of women with AMI was higher in cases with previous HD except MI. The proportion of AMI patients with an admission delay of  $\leq 12$  h was greater among patients with previous MI.

The prevalence of angina pectoris and hypertension did not differ between AMI and non AMI patients. A history of cardiac failure was more common in non AMI patients as well as treatment with digitalis and diuretics.

The CCU and total hospital mortalities from AMI were 16 and 21% respectively. These figures were significantly higher than the corresponding values (2 and 6%) in the non AMI group. However, the mortality among AMI and non AMI patients without previous HD was not significantly different. AMI patients with previous MI had a higher mortality than the rest and the total hospital mortality was lower (12%) among AMI patients without previous HD.

The average size of the MI evaluated from maximum S-ASAT was larger in patients without previous HD and smaller in those with acute myocardial infarction.

### Arrhythmias in the various diagnostic groups

All but two arrhythmias, viz. bradycardia and AF on admission, were more common in the AMI than in the non AMI group (Table II). In patients with previous MI the incidence of VF and AV block

Table I Some clinical and laboratory data on 679 patients with proven or non proven AMI

	AMI total (n=339)	AMI with previous		AMI without previous HD (n=94)
		MI (n=95)	HD except MI (n=150)	
Age (y) <sup>a</sup>	66±9*	67±7	68±**	63±10 :
Monitoring time (h) <sup>a</sup>	72±36***	73±38***	71±38***	72±31*
Sex ratio (♂/♀)	2 2	4 6,	1 1...	3 7,
Admission delay ≤12 h (%)	79	89..	69...	83
Previous angina pectoris (%)	46	58	68*	0
Previous hypertension (%)	32	26	56*	0
Previous cardiac failure (%)	11	19..	13	0
Previous diabetes mellitus (%)	10	10	11	10*
Digitalis on admission (%)	27	51...	26	4
Diuretics on admission (%)	30	44..	39	1
β blocker on admission (%)	17	17	26...	1
CCU mortality (%)	16***	23**	15**	11
Total hospital mortality (%)	21***	31***	21***	12,
S ASAT <sub>max</sub> (μkat/l)	3 8±2 6	3 2±2 2,	3 8±2 5	4 4±2 9,

\* Mean ± S D

Statistical significance at the 5, 1 and 0.1% level is indicated by \*, \*\* and \*\*\* respectively. Upper position indicates that statistical analyses were performed between corresponding groups (classes) of patients with and without AMI. Lower position of asterisks indicates that statistical analyses were performed between one subclass of patients of AMI and non AMI patients respectively.

II-III was not significantly different between those with and without AMI (Figs 1 and 2). In patients with previous HD except MI, AMI was associated with a significantly higher incidence of AF appearing after admission, whereas the incidence of VF

R on T VBs and ventricular bigeminy did not differ between patients with and without AMI (Figs 1 and 2).

There were relatively small differences in the rhythmia incidence between the various LQ

Table II Arrhythmia incidence estimated from analysis of computer generated alarm write-outs in CCU patients and mortality related to arrhythmia incidence

	Arrhythmia incidence (%)		Mortality (%)			
	AMI (n=339)	Non AMI (n=340)	AMI		Non AMI	
			CCU	Total hospital	CCU	Total hospital
Asystole	7**	2	83...	83...	83...	83,
VF	6*	2	42..	47..	50	50
VT <sub>120</sub>	38***	10	20	26	9	17
VT <sub>100</sub>	43***	14	14	20	4	11
RIR	33***	7	15	19	0	4
Extreme bradycardia	11	6	61***	61***	5	5
Paired VBs	72***	38	13*	18*	3	9
R-on T VBs	15*	7	8	13	0	0
Ventricular bigeminy	31**	20	13**	19	0	7
SVT	50***	22	10*	17*	1	1
More than 5 VBs/min	49***	29	18***	24**	1	8
More than 5 SVBs/min	45***	28	16*	24**	3	9
Bradycardia	39	45	16**	19***	4	5
Tachycardia	55***	34	20**	28***	6..	10
AV block II-III	12***	4	36..	43...	7	13
AF (on admission)	13	15	28*	42***	6	10
AF (SR on admission)	9***	3	20	23	0	11

Symbols and statistical analyses as in Table I. Lower position of asterisks indicates that statistical analyses were performed between patients with and without arrhythmias in the two diagnostic groups.

with previous HD except MI (n=150)	Non AMI without previous or present HD (n=49)
64±10	53±8...
43±31	30±18.
16	25
71	73
49	0
38	0
19	0
12	0
38	0
35	2
20	4
2	2
5	2

in AMI (Figs 1 and 2) Bradycardia, extreme bradycardia and frequent VBs were more common in patients with a history of MI. Most other arrhythmias were less common in patients with previous HD except MI, but the difference was not statistically significant (Fig. 1).

In the non AMI group patients without previous or present HD had a significantly lower incidence of VT paired VBs, R on T VBs, ventricular bigeminy, SVT and frequent VBs than those with HD (Figs 1 and 2). All ventricular arrhythmias were more common in patients with previous MI than in those suffering from other HD, even though the possible statistical significance was not tested.

As to the ventricular arrhythmias, the proportion of patients whose arrhythmias occurred during the first 12 h of monitoring ranged from 0.65 to 0.77 (Table III). Somewhat lower figures were usually found in the non AMI group. The proportion of patients with extreme bradycardia and more than 5 SVBs/min occurring during the first 12 h was relatively low (<0.40) and essentially similar in AMI and non AMI patients.

Of patients with asystole, VF or AV block II-III, 10-67% had their first arrhythmia episode in the last hour of monitoring (Table III). Such arrhythmias were always fatal. In the AMI group, extreme bradycardia also belonged to arrhythmias often recorded terminally.

#### Hospital prognosis in the arrhythmias studied (Table II)

The mortality among patients with asystole was about 80% and among those with VF about 50%.

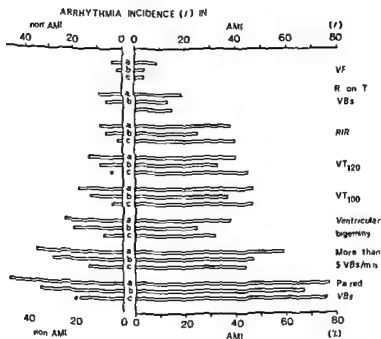


Fig. 1 Incidence of ventricular arrhythmias in subclasses of patients with proven and non proven AMI. a = History of previous MI, b = history of previous HD except MI, c = no previous or present HD. Statistical analyses at the 5% (\*), 1% (\*\*) and 0.1% (\*\*\*) level performed between one subclass of patients within each arrhythmia group and the rest of AMI and non AMI patients respectively.



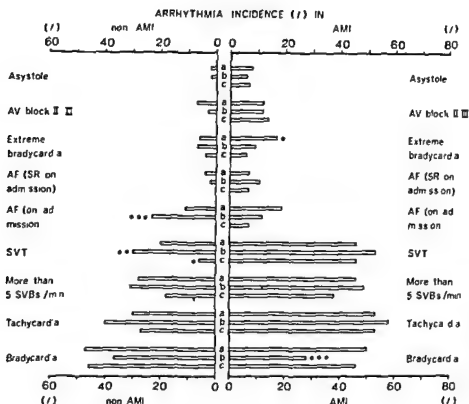


Fig. 2 Incidence of studied arrhythmias in patients with and without AMI. Symbols analyses as in Table I.

and no difference was observed between patients with and without AMI. Regarding VT<sub>120</sub>, VT<sub>100</sub>, RIR, R-on T VBs, AV block II-III and AF appearing after admission there was no significant difference in mortality between AMI and non-AMI patients, even though the absolute values were higher in the AMI group. The other arrhythmias studied

were associated with a higher CCI among AMI than non-AMI patients.

In the AMI group, the CCU mortality among patients with asystole, VI, bradycardia, tachycardia and AV block, among those without these arrhythmias, total hospital mortality was considered

Table III Proportion of arrhythmias occurring during the initial 12 hours of monitoring and last hour of monitoring

	Arrhythmia during first 12 h		Arrhythmia during last h	
	AMI	non AMI	AMI	non AMI
Asystole	0.48	0.67	0.43	0.67
VF	0.68	0.63	0.11	0.13
VT <sub>120</sub>	0.67	0.56	0.02	0.00
VT <sub>100</sub>	0.66	0.57	0.01	0.02
RIR	0.72	0.58	0.01	0.04
Extreme bradycardia	0.33	0.29	0.19	0.05
Paired VBs	0.77	0.74	0.01	0.03
R-on T VBs	0.65	0.60	0.00	0.04
Ventricular bigeminy	0.69	0.60	0.02	0.03
SVT	0.46	0.53	0.01	0.01
More than 5 VBs/min	0.76	0.77	0.00	0.03
More than 5 SVBs/min	0.39	0.37	0.03	0.03
Bradycardia	0.74	0.70	0.05	0.00
Tachycardia	0.54	0.71	0.02	0.03
AV block II-III	0.41	0.80	0.12	0.15

also turned out to be an ominous sign. The mortality in AMI was significantly lower in patients with paired VBs and SVT. The finding was, however, not confirmed when the hospital mortality was considered. No difference in mortality was observed between AMI patients with or without VT<sub>1</sub>, comparing the non AMI patients only those with paired VBs or tachycardia had an increased mortality compared to the rest.

## DISCUSSION

The analysis of arrhythmia incidence in the CCU had the primary purpose of this study. The prognostic implications of various arrhythmias were studied as a secondary goal.

The total monitoring time for the 679 patients was 4 h. However, the ECGs from all 850 patients (monitoring hours) had to be analysed, since the routine of write-outs was performed without any information on the patients. A manual beat analysis of a slow speed paper record from all patients would be a very time consuming task. The application of the automated system was an advantage. To my knowledge, the capacity of the system has not previously been utilized in clinical research. Computer assisted analysis of ECG material could be used in a study of the different types, but data collection and analysis would be very laborious.

The application of the monitoring system seemed justified in view of results from a previous evaluation (2), showing that about 90% of patients with ventricular and supraventricular arrhythmias recognized after scrutiny of alarm write-outs during VT<sub>120</sub>. 79% of mixed CCU patients with arrhythmia were identified and all patients with asystole and VF had at least one of these lesions reproduced on the write-outs (11). However, the number of patients with the last mentioned arrhythmias was small.

The incidence of arrhythmia among a large number of AMI patients has not been presented earlier. Jensen (27) analysed arrhythmia incidence during the first 24 h in the CCU using a continuous ECG recording for arrhythmia documentation. He applied a restrictive policy for the administration of digoxin and observed VT (2 or more VBs with a frequency >100) in 65% of 37 AMI and in 12% of 43 non AMI patients. For frequent VBs (more than

5/min) consecutive VBs (2 or more in succession) and R on T VBs his corresponding figures in the two diagnostic groups were 62 and 19%, 81 and 28%, and 59 and 2% respectively. Apart from the high incidence of R on T VBs, these figures were only slightly higher in the AMI group and somewhat lower in the non AMI group compared to the present findings. R on T VBs were analysed in the present study only at this alarm, which partly explains the relatively low incidence of this arrhythmia.

The majority of patients with arrhythmias in the AMI and non AMI groups had their first arrhythmia within the first 12 h of monitoring (Table III). Thus, the longer monitoring time in AMI patients (Table I) probably did not contribute markedly to the higher arrhythmia incidence in AMI compared to non AMI patients.

A short admission delay of AMI patients and extensive infarction are associated with a higher incidence of ventricular arrhythmias (4, 26). AMI patients with previous MI had a shorter admission delay but smaller infarctions on the average. Thus, the influences of these factors on arrhythmia incidence might have cancelled out each other. AMI patients with previous HD had a higher mean age, lower male:female quotient, longer admission delay, higher incidence of previous angina pectoris and hypertension, and used  $\beta$  blockers more frequently than the rest of the AMI patients. One or more of these findings could possibly explain the slightly lower incidence of most ventricular arrhythmias observed in AMI patients with previous HD except MI (Fig. 1).

The incidence of cardiac arrhythmias in AMI has been reported in a great number of publications in the last 15 years (1, 10, 15, 16, 19, 23, 25, 26, 31, 32, 33, 38, 40). Several factors such as selection of patients, definition of arrhythmias, admission delay, principles for antiarrhythmic treatment may influence arrhythmia incidence in the CCU. The length of and methods for arrhythmia monitoring have varied. The above circumstances complicate a comparison between the earlier and the present results. Below, however, some findings will be discussed and related to earlier results in AMI patients.

**Asystole.** Ten of 23 cases with asystole (R-R > 5.0 sec) in the present study had their first asystole episode within one hour prior to death. Four out of the other 13 patients survived their stay in hospital.

Table IV Ventricular tachycardia in AMI during CCU stay reported in some studies

	Principal method for arrhythmia documentation	Studied period of CCU stay	Maximal admission delay (h)	No of cases	CCI before?
Spann et al (38)	Arrhythmia detector	Total	30	30	+
Julian et al (16)	Oscilloscope monitoring	Total	48	100	II
Lown et al (23)	Oscilloscope monitoring	Total		300	II
Bashour et al (1)	Taped ECG avionics system	First 24 h	18	30	
Dalle et al (5)	Oscilloscope monitoring + R-R detector	First 96 h		300	
Mogensen (26)	Oscilloscope monitoring	Total		421	II
Mogensen (26)	Continuous ECG recording	First 24 h		37	
de Souza et al (37)	Taped ECG avionics system	First 24 h	24	52	
Henning & Lundman (10)	Oscilloscope monitoring	First day in CCU		1 831	II
Löfmark & Orinius (24)	Oscilloscope monitoring	Total		274	+
Present study	Computer-generated alarm write-outs	Total	96	339*	II

- \* Patients with shock, higher degrees of AV block and abundant supraventricular arrhythmias were excluded.  
 • Patients with an uncertain admission delay were excluded.

Asystole (R-R >3.0 sec) and excluding terminal events have been reported in 7% of AMI patients, a total hospital mortality of 75% (26).

**Ventricular fibrillation.** Transient self-terminating forms of VF were observed in one AMI and two non-AMI patients. Such episodes constituted 5 and 25% of first VF in AMI and non-AMI patients respectively. The incidence of VF in the present material (6%) lies near the middle of the incidence (1–16%) reported earlier in AMI (16, 17, 20, 23, 25, 26, 31, 32, 40).

Five out of 19 patients had their first VF episode without earlier signs of heart failure or hypotension (primary VF). The first VF only rarely ended fatally (Table III). Six patients with later proven AMI were defibrillated before arrival at the CCU. Four out of these 6 episodes of VF were considered primary. If these 6 cases were added to those previously reported, the total hospital mortality in primary VF, secondary VF and all VF was 11, 56 and 40% respectively. These figures are somewhat lower

than those reported by Lawrie et al (6). Mogensen (26). Two non-AMI patients had exclusively before admission, both survived hospital stay.

**Ventricular tachycardia.** The incidence in the present and some earlier studies is shown in Table IV. In 1967 Lown et al (23) presented for the value of lignocaine in so-called frequent or multiform VBs (runs of VBs, R-on-T, VT) in AMI. This type of treatment, given in order to prevent VT, is generally accepted and practised in the present (10, 23, large series 26). As a prophylactic, lignocaine reduces the incidence of VT in AMI (30). The indications for antiarrhythmic treatment must also be considered when comparing Table IV. In two studies (24, small series) lignocaine was given only when VT or post-VT was detected. However, even though many factors influence the incidence of VT, the high frequency served for runs of VBs (VT) in the present

## tachycardia

Rate above (min <sup>-1</sup> )	Incidence (%)	CCU mortality (%)
100	37	27
	6	67
70	28	20
99	50	
100	18	47
50	40	16
100	65	
100	52	
100	30	30
50	41	
40	65	21
100	57	21
120	38	26

ly reflect a high sensitivity of the automated monitoring system to this arrhythmia. In previous studies have indicated that VT is a harbinger of serious complications in AMI (5, 19, 24, 26, 31, 40). This observation was not noted in the present series despite stricter criteria for the definition of VT<sub>10</sub> compared to used by most other authors. In fact, in the present study only AMI patients with 8 or more runs in succession with a rate of >120/min had a poor CCU and total hospital prognosis ( $p < 0.01$ ) compared to those with no or other runs of VEs. It is conceivable that short and single episodes of VT were overlooked in previous studies whereas runs with higher rates carrying a poorer prognosis were detected. As pointed out by Stock (40), an improved quality of arrhythmia monitoring will influence the prognostic value of other arrhythmias.

**Supraventricular arrhythmias** RIR was observed in 33% of the present AMI patients. Other studies (34, 37, 38, 41), using slightly different

diagnostic criteria reported this arrhythmia in 13–36% of their patients. The benign character of RIR has also been documented earlier (34).

Paired VEs was the most common arrhythmia in AMI in this study and the incidence of 72% certainly is one of the highest observed. Paired VEs turned out to be a favourable prognostic sign in AMI and patients with this arrhythmia had a significantly better CCU prognosis than those without. A similar observation was made by Julian et al. (16) who found that patients with a low number of VEs during the CCU stay had a better prognosis than those without VEs.

R-on T VEs were recorded in 15% of the present AMI patients compared to 2–9% of patients monitored on oscilloscopes (16, 19, 26, 31) and to 10–49% of patients whose ECGs were taped and analysed off line (1, 6).

In some previous studies the majority of ventricular arrhythmias (paired VEs, R-on T VEs and frequent VEs) were associated with an increased mortality (16, 19, 26). This observation was not confirmed in the present study, probably due to an increased detection rate of relatively benign arrhythmias.

**Supraventricular tachyarrhythmias** Other authors report an incidence of 33–50% in tachycardia (sinus or supraventricular rhythm with a rate of >100/min) with a hospital mortality of 28–52% (15, 16, 26). An even higher incidence (55%) was found in the present series despite a stricter definition (HR > 120/min) and the poorer prognosis for these patients was confirmed. However, the relationship between increased mortality and the presence of tachycardia did not persist if patients with AF and tachycardia were excluded from all cases with tachycardia.

SVT or atrial tachycardia has been reported at a rate of 2–11% (15, 16, 19, 23, 25, 26) but no clear diagnostic criteria were given. In two series SVT was defined as three or more consecutive SVBs with a rate of >100/min and was found in 4% with the use of conventional monitoring (22) and in 29% from continuous ECG recording (21). In the latter report patients with AF were excluded and the same procedure reduced the SVT rate from 50 to 37% in the present material. Thus it appears that the monitoring methods used by most previous investigators were insensitive to short runs of SVBs but different diagnostic criteria could also contribute to the low incidence of SVT.

reported in some series. The benign character of this arrhythmia has been recognized earlier (22-23). In the present series patients with SVT had a significantly better CCU prognosis than those without. However, this effect did not remain significant when the total hospital mortality was considered, even after exclusion of patients with concomitant AF.

Atrial fibrillation and flutter were not separated in the present study for two reasons. Firstly, a differentiation from a single lead recording may be impossible; secondly, transitional forms are common. The incidence of AF in this study as well as the poorer prognosis for patients with this arrhythmia compared to those with SR are in line with earlier results (3, 9, 14, 18, 22, 39). However, the better prognosis for patients developing AF compared to those with AF on admission has not been stressed earlier.

**Bradycardias (AV block II-III).** Bradycardia was observed in 39% of the present AMI patients. In this group no significant relationship was observed between the occurrence of bradycardia and treatment with digitalis or  $\beta$  blockers prior to or during the CCU stay. In the non-AMI group bradycardia was the most common arrhythmia (45% of all cases). Bradycardia (supraventricular rhythm <50/min) has been noted by other investigators with a frequency of 11 and 21% (25, 26). No figures regarding the incidence of bradycardia in non-AMI patients have been reported earlier.

Conflicting results regarding the prognostic importance of bradycardia have been reported, with a higher (26) or a lower (15, 19, 23) mortality rate than average among patients with AMI. In the present study a HR of 35-50/min was not related to an increased risk for the patient, whereas extreme bradycardia (HR <35/min) was an ominous sign in AMI but as to outcome of little importance in non-AMI patients. In the latter group extreme bradycardia was noted in 21 cases, in 16 in association with extreme supraventricular bradycardia (slow SR, atrial or nodal origin) with a 6% mortality and in 5 cases in association with AV block II-III with a 20% mortality. Extreme bradycardia was noted in 36 AMI patients, in 13 associated with extreme supraventricular bradycardia (mortality 38%), in 15 with higher degrees of AV block (mortality 47%) and in 8 with an idioventricular rhythm with no or an irregular atrial activity (mortality 100%). Thus the very slow rhythms, irrespective of

type, carried a poorer prognosis in AMI than in non-AMI patients, although the relatively small number of patients did not permit an accurate statistical analysis. Slow supraventricular and non-AMI patients were relatively benign; the proportion of terminal bradyarrhythmias partly explained the very high mortality in bradycardia in this patient group.

**Lignocaine treatment.** In the present study lignocaine by infusion was given to 21% of AMI and 2% of non-AMI patients, whereas 46 and 50% respectively fulfilled the criteria of Lown et al. (23) for prophylactic treatment. Lignocaine VF and VT<sub>1-2</sub> were diagnosed in 70% respectively of AMI patients treated with lignocaine. VT<sub>1-2</sub> was found in 30% of AMI patients not receiving this drug and in 81% of those receiving it; only one episode of VT<sub>1-2</sub> was documented in patients not receiving it, contrasting with 27% of patients receiving it. The restrictive use of lignocaine had an obvious negative influence on the detection of VT<sub>1-2</sub>, probably influenced the incidence of VT<sub>1-2</sub> to a minor degree only. A few patients received only the bolus dose of lignocaine, but the results for patients for whom this drug was considered necessary or contraindicated was not reliable. The more restrictive use of antiarrhythmic drugs is justified with efficient ECG monitoring. (7) recently suggested general lignocaine prophylaxis in AMI, partly due to a relative inefficiency of conventional ECG monitoring.

**Uncertain interpretation regarding VT.** In the present study was noted specifically. Based on the information minimum and maximum values, the incidence of VT could be calculated for AMI patients: the minimum value for VT<sub>1-2</sub> was 10%, the maximum 41% and for VT<sub>1-3</sub> 40 and 35% respectively. In the non-AMI group the corresponding figures for VT<sub>1-2</sub> were 9 and 12% and for VT<sub>1-3</sub> 14 and 14%. Thus questionable VTs were rather few patients and a change in the diagnostic policy concerning questionable beats may have influenced markedly the incidence of VT.

Apart from arrhythmias, other circumstances may influence the prognosis during the stay in CCU. Some factors adversely affecting the prognosis in AMI are: high age (8, 10), bundle branch block (26, 40), heart failure (17, 35), cardiomegaly (29) and extensive myocardial damage. In the present study these factors showed significant relationships with the prognosis in several of the arrhythmias studied.

sent study the prognosis has been estimated by a qualitative analysis of arrhythmias as a factor in the development of an estimation of prognosis in various combinations of arrhythmias as in the CCU.

Also arrhythmias preceding the most serious events should be studied. The high incidence of ventricular and supraventricular arrhythmias in AMI was confirmed and compared to a material of nearly equal size. The prognostic implications regarding the arrhythmias probably valid for CCUs with efficient monitoring.

## REFERENCES

our F A, Jones E & Edmonson R. Cardiac arrhythmias in acute myocardial infarction. II. Incidence of the common arrhythmias with special reference to ventricular tachycardia. *Dis Chest* 51: 570 (1976).

H C. An analysis of the time relationships in myocardial infarction. *Heart* 7: 353 (1970).

tal N, Peterburg I & Szwarcberg (Shahar) J. Atrial fibrillation developing in the acute phase of myocardial infarction. Prognostic implications. *Chest* 70: 109 (1976).

J Roberts R, Ambros D, Oliver C & Sobel B. Relations between enzymatically estimated myocardial infarct size and early ventricular dysrhythmia. *Circulation* (Suppl) 1: 150 (1976).

X S, Meltzer E & Kravitz B. A new look at ventricular tachycardia. *Acta Cardiol* 22: 519 (1968).

enf N, Myerburg R, Scherlag B, Befeler J, Randall J, Castellanos A & Lazzara R. Electrophysiological antecedents of primary ventricular tachycardia. Value of the R-on-T phenomenon in myocardial infarction. *Br Heart J* 38: 415 (1976).

D C. Should lidocaine be administered early to all patients after acute myocardial infarction? (Editorial) *Circulation* 58: 581 (1978).

ers C. Short and long term prognostic indices in acute myocardial infarction. *Acta Med Scand* 193: 555 (1973).

C Lundman T, Mogensen L, Ornnus J, Jørgensen A & Wester P O. Atrial fibrillation in myocardial infarction. *Acta Med Scand* 193: 39 (1973).

ng R & Lundman T. Swedish co-operative study. *Acta Med Scand* (Suppl) 586: 1975.

ng J. Detection of asystole, ventricular fibrillation, ventricular tachycardia with automated ECG monitoring. *Acta Med Scand* 205: 17 (1979).

lcaton and evaluation of automated arrhythmia monitoring in the coronary care unit. *Acta Med Scand* (Suppl) 630: 1979.

ng J & Nygård M E. Accuracy of arrhythmia alarms from a computer based arrhythmia monitoring system. *Acta Med Scand* 203: 153 (1978).

D Sloman G & Penington C. Effects of

atrial fibrillation on prognosis of acute myocardial infarction. *Br Heart J* 40: 303 (1977).

15 Jewitt D E, Balcon R & Raftery E B. Incidence and management of supraventricular arrhythmias after acute myocardial infarction. *Lancet* 7: 734 (1967).

16 Julian D G, Valentine P A & Miller G G D. Disturbances of rate, rhythm and conduction in acute myocardial infarction. A prospective study of 100 consecutive unselected patients with the aid of electrocardiographic monitoring. *Am J Med* 37: 915 (1964).

17 Kill P T & Kimball J T. Treatment of myocardial infarction in a coronary care unit. A two year experience with 750 patients. *Am J Cardiol* 20: 457 (1967).

18 Klass M & Haywood J. Atrial fibrillation associated with acute myocardial infarction. A study of 34 cases. *Am Heart J* 79: 757 (1970).

19 Lawrie D M, Greenwood T W, Goddard M, Harvey A C, Donald K W, Julian D G & Oliver M F. A coronary-care unit in the routine management of acute myocardial infarction. *Lancet* 2: 109 (1967).

20 Lawrie D M, Higgins M R, Godman M J, Oliver M F, Julian D G & Donald K W. Ventricular fibrillation complicating acute myocardial infarction. *Lancet* 7: 523 (1968).

21 Lesser L. Atrial tachycardia in acute myocardial infarction (letter). *Ann Intern Med* 86: 59 (1977).

22 Libberthson R, Salisbury K, Hutter A & De Sanctis R. Atrial tachyarrhythmias in acute myocardial infarction. *Am J Med* 60: 956 (1976).

23 Lown B, Vassault C, Hood W, Fakhro A, Kaplaninsky E & Roberge G. Unresolved problems in coronary care. *Am J Cardiol* 20: 494 (1967).

24 Lofmark R & Ornnus E. Restricted lidocaine prophylaxis in acute myocardial infarction. *Acta Med Scand* 201: 89 (1977).

25 Meltzer L E & Kitchell J B. The incidence of arrhythmias as associated with acute myocardial infarction. *Prog Cardiovasc Dis* 9: 50 (1966).

26 Mogensen L. Ventricular tachyarrhythmias and lidocaine prophylaxis in acute myocardial infarction. *Acta Med Scand* (Suppl) 513: 1970.

27 —. Ventricular arrhythmias and myocardial infarction (Swedish). Proceedings of symposium on Ventricular arrhythmias in myocardial infarction. pp 21-31. Hassle, Mölndal 1975.

28 Nygård M E & Hulting J. A system for automated ECG monitoring. *Comp Biomed Res* 12: 181 (1979).

29 Nyquist O. Shock complicating acute myocardial infarction. *Acta Med Scand* (Suppl) 536: 1977.

30 Pitt A, Lipp H & Andersson S T. Lidocaine given prophylactically to patients with acute myocardial infarction. *Lancet* 1: 617 (1971).

31 Raftery E B, Rehman M F, Banks D C & Oram S. Incidence and management of ventricular arrhythmias after acute myocardial infarction. *Br Heart J* 31: 773 (1969).

32 Restaux N, Bray C, Bullard H, Murray M, Robinson J, Bridgen W & McDonald L. 150 patients with cardiac infarction treated in a coronary unit. *Lancet* 1: 1785 (1967).

- 33 Rothfeld E L Bernstein A Parsonnet V Zucker I R & Alinsonorn C A Telemetric monitoring of the electrocardiogram in acute myocardial infarction *Dis Chest* 51 193 1967
- 34 Rothfeld E L Zucker I R Parsonnet V & Alinsonorn C A Idioventricular rhythm in acute myocardial infarction *Circulation* 37 203 1968
- 35 Sjögren A Left heart failure in acute myocardial infarction *Acta Med Scand (Suppl)* 510 1970
- 36 Sobel B Bresnahan G Shell W & Yoder R Estimation of infarct size in man and its relation to prognosis *Circulation* 46 640 1972
- 37 de Soyza N Bissett J Kane J Murphy M & Doherty J Ectopic ventricular prematurity and its relationship to ventricular tachycardia myocardial infarction in man *Circulation* 1974
- 38 Spann J F Moellering R C Wheeler E O Arrhythmias in acute myocardial infarction *N Engl J Med* 271 427 1964
- 39 Stannard M & Sloman J G Atrial fibrillation in acute myocardial infarction *Med J Aust* 1967
- 40 Stock E Goble A & Sloman J G Atrial fibrillation in cardiac infarction *Br Med J* 1967
- 41 Talbot S & Greaves M Association of extrasystoles and ventricular idioventricular rhythm *Br Heart J* 38 400

# Intraaortic Balloon Pumping in the Treatment of Cardiogenic Shock Complicating Acute Myocardial Infarction

G Forssell R Nordlander O Nyquist and K. Schenck Gustavsson

From the Department of Medicine Karolinska Institute at Huddinge Hospital Huddinge Sweden

**ACT** A 5.1% incidence of cardiogenic shock occurred in a consecutive series of 680 patients with myocardial infarction (AMI) during a five year period. The hospital mortality was 94%. Shock was treated according to a stepwise policy including assisted circulation with intraaortic balloon pumping. During the five-year period, only five patients (0.7%) of the shock patients, had shock for more than 24 hours (the minimal time for attempting therapy and preparing for assisted circulation). All patients were below 75 years of age and without terminal diseases. Together with ten AMI patients in the study, 15 patients were given IABP during 1-318 hours (mean 58). Shock was reversed in 12 (80%) of the patients and five (33%) could be weaned off and discharged from the CCU. However, only 10 patients (13%) were long term survivors.

**Key words:** acute myocardial infarction, intraaortic balloon pumping, assisted circulation, cardiogenic shock—treatment—mortality.  
Acta Med Scand 206 189-192 1979

Complicating acute myocardial infarction still accounts for a major proportion of the mortality of AMI. Much effort has therefore been made to reduce the mortality of cardiogenic shock during recent years especially by use of mechanical circulatory support. The present report describes cardiogenic shock and assisted circulation in a consecutive series of patients with AMI seen in the coronary care unit (CCU) during a five year period.

## PATIENTS AND METHODS

The study population consists of (A) all patients with AMI admitted to the CCU from Sept 1972 to Sept 1977 (B) all patients with cardiogenic shock secondary to AMI re-

ferred from other hospitals for assisted circulation. (C) patients with shock and AMI treated with assisted circulation in another hospital during the period Dec 1970 to Dec 1971. The criteria for the diagnosis of AMI were 1) ST segment elevation in two or more of the 12 ECG leads 2) Two sASAT values of 0.67  $\mu$ kat/l or more and with a maximum about 24 hours after onset of symptoms in combination with lower sALAT values 3) Autopsy findings of myocardial necrosis of an age corresponding to the onset of symptoms.

1) Appearance of a pathological Q wave and/or appearance or disappearance of a localized ST elevation followed by a T inversion in two or more of the 12 ECG leads 2) Two sASAT values of 0.67  $\mu$ kat/l or more and with a maximum about 24 hours after onset of symptoms in combination with lower sALAT values 3) Autopsy findings of myocardial necrosis of an age corresponding to the onset of symptoms.

Shock was defined as a palpatory systolic BP below 90 mmHg for more than half an hour in association with at least three of the following findings:

1) Signs of reduced cerebral circulation such as mental confusion or unconsciousness 2) Signs of reduced peripheral circulation such as cold skin 3) Signs of impaired renal circulation with a urine flow of less than 20 ml/hour 4) Peripheral or general cyanosis 5) Metabolic acidosis.

Patients fulfilling the above criteria of shock were treated according to the following stepwise policy:

1) Correction of arrhythmias 2) A slightly head-down posture (except for cases of frank pulmonary oedema) 3) Oxygen 10 l/min by mask or nasopharyngeal catheter 4) Methylscopolamine i.v. when the heart rate was below 80/min 5) Correction of acidosis 6) Rapid infusion of 300 ml 5.5% glucose if frank pulmonary oedema or signs of elevated central venous pressure were not present 7) Assisted circulation to patients below 75 years of age without other disabling or terminal diseases.

Assisted circulation was performed by means of an intraaortic balloon pumping (IABP). The AVCO system with a three segmental balloon was used in patient groups A and B (defined above) and a monosegmented balloon and the Milton Roy Company driving unit in the patients of group C. The balloon catheter was inserted into the femoral artery bedside in the CCU after local anaesthesia. Inflation and deflation of the balloon were adjusted ac-

**Abbreviations:** AMI = acute myocardial infarction IABP = intraaortic balloon pumping CCU = coronary care unit



Table 1 Patients with cardiogenic shock secondary to AMI treated with IABP

A=anterior L=lateral I=inferior VSD=ventricular septal defect AA=aortic aneurysm X=in shock

Case no	Age (y)	Previous myocardial infarction	ECG site of AMI	Hours from onset of symptoms to shock	Hours in shock	Hours from shock to start of IABP	Hours of IABP	Shock disappeared	Termination of IABP/CCU survival	h
<b>Group A</b>										
1	64	-	A L	49	15	12	36	-	+	+
2	70	-	A L I	10	11	6	318	+	-	-
3	70	+	A	48	26	8	58	+	+	-
4	73	-	I L	12	15	4	11	-	-	-
5	58	-	A	1	5	4	28	+	+	-
<b>Group B</b>										
6	70	+	A L I	X	9	8	1	-	-	-
7	60	-	A L I	X	14	10	19	+	-	-
8	60	-	A L	X	27	15	12	-	-	-
9	71	-	A L	X	10	7	10	+	-	-
10	60	+	A L I	X	70	7	85	+	-	-
<b>Group C</b>										
11	74	+	I L	X	21	5	68	+	-	-
12	71	+	I	67	23	3	90	+	+	-
13	69	-	I L	X	37	2	41	+	-	-
14	67	-	A	X	8	3	17	+	-	-
15	68	-	I L	5	12	1	80	+	-	-

according to the aortic pressure curve. Details of the techniques have been described elsewhere (4).

Conventional statistical methods have been used for calculation of the arithmetic mean and standard deviation. Significance of differences between mean values was tested by Student's *t*-test.

## RESULTS

### Group A

During the five year period Sept 1972–Sept 1977 680 consecutive patients with AMI were admitted to the CCU (Fig 1). Fourteen (2.1%) were in shock already on admission and 21 (3.1%) developed shock later during their CCU stay. In all 35 patients (5.1%) with a mean age of 70 years were in shock. The mean age of the 645 patients without shock was 67 years. The difference is not statistically significant.

Sixty per cent of the shock patients developed shock 1–96 hours (mean 22) after admission to the CCU. The shock lasted for 1–37 hours (mean 8) for less than 3 hours in 15 patients. One of these 15 patients had a rapid atrial fibrillation. Shock symptoms disappeared after electroconversion and the patient was discharged alive from hospital.

The other 14 patients died in shock. 11 patients who had shock for more than 3 h more than 75 years old. Shock never appeared after electroconversion of a tachycardia in one of them but the patient died six days later.

Five of the eight patients aged 70 or less and shock for more than 3 hours received circulation with IABP (Table 1). The other 11 patients who were not treated with IABP died due to other terminal diseases.

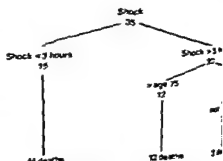


Fig 1 Outcome after treatment of cardiogenic shock in 35 shock patients during 5 year period.

3P  
 1  
 shock disappeared  
 2  
 IABP terminated  
 discharged from CCU  
 1  
 long term survivors  
 outcome in 15 patients with shock complicating  
 treated with IABP

shock. The time from onset of shock to start IABP was 4-12 hours (mean 7). IABP was continued for 11-318 hours (mean 90). In four of the five patients, shock symptoms disappeared during the assisted circulation. One patient in whom shock symptoms remained throughout the IABP period had a large aortic aneurysm at autopsy. Three patients could be weaned off IABP. The balloon pump was extracted and they were all discharged from the CCU. Two of them died from reinfarction 19 days respectively after termination of assisted circulation. The third patient was discharged from hospital and returned to work. He died from reinfarction 3 years and 8 months later.

One patient (no. 2) was completely pump dependent. He had a ventricular septal defect which the surgeon declined to operate upon and died after 19 days of assisted circulation.

Of the 35 shock patients, 14 had complete AV block and/or periods of asystole during the shock. All died despite of transvenous pacemaker treatment. The survival time in shock for these 14 patients varied from 1-37 hours (mean 9). One patient was also treated with IABP.

Of the 35 shock patients, 14 had complete AV block and/or periods of asystole during the shock. All died despite of transvenous pacemaker treatment. The survival time in shock for these 14 patients varied from 1-37 hours (mean 9). One patient was also treated with IABP.

Of the 35 shock patients, 14 had complete AV block and/or periods of asystole during the shock. All died despite of transvenous pacemaker treatment. The survival time in shock for these 14 patients varied from 1-37 hours (mean 9). One patient was also treated with IABP.

Of the 35 shock patients, 14 had complete AV block and/or periods of asystole during the shock. All died despite of transvenous pacemaker treatment. The survival time in shock for these 14 patients varied from 1-37 hours (mean 9). One patient was also treated with IABP.

Of the 35 shock patients, 14 had complete AV block and/or periods of asystole during the shock. All died despite of transvenous pacemaker treatment. The survival time in shock for these 14 patients varied from 1-37 hours (mean 9). One patient was also treated with IABP.

died before IABP could be started. Five patients were treated with IABP for 1-85 hours (mean 25) (Table I). Shock symptoms disappeared in three but they all died in the CCU.

### Group C

Five patients with shock due to AMI were given IABP in the CCU of the Serafimer Hospital during a one year period 1970-71 (Table I). Assisted circulation was given during 17-90 hours (mean 59).

Shock was reversed in all patients during IABP which was terminated in two who could later be discharged from the CCU. One of these patients died from reinfarction outside hospital after four years.

Extensive myocardial necroses of varying ages were found in all autopsied shock patients.

## DISCUSSION

The incidence of cardiogenic shock in association with AMI was reported to be about 20% in the beginning of the CCU era. Considerably lower rates 4-8% have been found by others (3). In the present consecutive series there was a 5% incidence of cardiogenic shock during a five year period. Several explanations may be found for this reduced incidence: among others a change of the criteria for cardiogenic shock. Binder et al. (1) reported on the inverse relationship between incidence and mortality rate of shock: i.e. the lower the incidence, the higher the mortality. Another explanation may be a prevention of shock by better treatment of congestive heart failure, arrhythmias, fluid deficits and metabolic derangements.

In the present series, 14 of the 35 patients had terminal shock, that is for less than three hours prior to death. Thus the incidence of non-terminal shock was 3% and more than half of the non-terminal shock patients were above 75 years of age.

In the present study, the age of 75 years was regarded as a cut off age beyond which the patient was not considered for assisted circulation. If three hours are the assumed minimal time required for attempting medical therapy and preparing assisted circulation, only eight patients of the present consecutive five year series were candidates for assisted circulation.

The IABP was very effective in reversing the shock state—reversed in four of five patients (the fifth had a large aortic aneurysm). Among the 30

patients not given IABP shock was reversed in only two—after electroconversion of rapid arrhythmias in both.

Altogether 15 patients were treated with IABP (Fig. 2). In 12 (80%) of these shock was reversed and five (33%) could be weaned off assisted circulation and discharged from the CCU. However only two patients (13%) were long term survivors. These figures are in accordance with those reported by others (2). Although effective in treating the cardiogenic shock state IABP seems not to have changed the poor prognosis of shock in association with AMI.

Autopsy revealed extensive acute and old myocardial damage in all IABP treated and other shock patients. It is unlikely that any treatment medical or surgical could have saved these patients. The only way may probably be to start IABP as early as possible preferably before shock develops.

## ACKNOWLEDGEMENT

This study was supported by a grant from the National Association against Heart and Chest

## REFERENCES

- 1 Binder M J, Ryan J A, Jr, Marcus S H, Jr, Strange D & Agress C M. Efficacy in shock following acute myocardial infarction. *Med* 18: 622, 1955.
- 2 Jackson G, Cullum P, Pastello-Peckes A, Thur A & Jewitt D. Intra aortic balloon pump in cardiogenic shock after myocardial infarction: surgical treatment. *Br Heart J* 39: 598, 1977.
- 3 Kuhn L A. "Salvage" with assisted circulation in acute myocardial infarction and shock. *Acta Med Scand* 34: 873, 1974.
- 4 Nyquist O. Shock complicating acute myocardial infarction. A clinical hemodynamic and laboratory study. *Acta Med Scand* (Suppl) 536: 1972.

# Q Waves and Coronary Artery Disease

J. Fischer Hansen and O. Pedersen Bjergaard

From the Medical Department B, Rigshospitalet, Copenhagen, Denmark

**CT.** In a consecutive series of 234 patients for selective coronary arteriography 78 pathological Q waves. In 32 of these 78 patients showed left ventricular hypertrophy, QRS of  $\geq 0.12$  sec, incomplete left bundle branch, left axis deviation. Fourteen (44%) of these 32 had coronary artery disease (CAD), while of the remaining 46 patients without these changes had CAD ( $p < 0.0005$ ). Among the 46 34 of 35 with angina pectoris had CAD, 4 to 6 of 11 without angina pectoris ( $p < 0.0005$ ). Our study thus shows that Q waves may be predictors of CAD especially in patients with angina pectoris.

**Ischemic myocardial infarction, angina pectoris, arteriography, ischemic heart disease, Q waves.**  
Acta Med Scand 1979; 206: 193-197.

pathological Q waves are normally considered indicative of a myocardial scar following acute myocardial infarction due to coronary atherosclerosis. In studies from recent years demonstrated normal coronary arteries in several with previous acute myocardial infarction, therefore several causes of myocardial infarction other than coronary atherosclerosis have been cited (1). The purposes of this investigation were to determine the predictive value of pathological Q waves for diagnosis of coronary artery disease (CAD), to describe ECG changes where Q waves are indicative of CAD.

## PATIENTS AND METHODS

73 technically satisfactory selective coronary arteriographies were performed in our department in 1974. A detailed report has previously been published concerning lead catheters and complications of coronary arteriography (5). All investigations carried out with Judikathode (9) were performed for diagnostic reasons; coronary surgery was not available in our hospital at the time.

Fastening supine 12-lead ECGs were assessed in accordance with the Minnesota code (18). Pathological Q waves fulfilled the code points 1, 2, 1, 2 or 1, 3. The ECGs were evaluated by two observers independently; the results were compared and disagreements solved by mutual consent.

The following definitions were used in the analyses: 1) left ventricular hypertrophy = points 3, 1 and 3, 3; 2) left axis =  $30^\circ$  through  $90^\circ$  in leads I, II, III (point 1); 3) right bundle branch block (RBBB) = point 7, 2; 4) intraventricular block = point 7, 4; 5) incomplete left bundle branch block (LBBB) = 7, 6 and included patients with left hemiblock (19). None of the patients had right ventricular hypertrophy.

The degree of stenosis of a coronary artery has been assessed in the project on where the stenosis is most pronounced (6). CAD denotes more than 75% stenosis in one of the major coronary arteries, the right coronary artery, the circumflex or the anterior descending branch of the left coronary artery. None of the patients had left main CAD.

$\chi^2$  test and Fisher's test were used for statistical comparison between groups.

## RESULTS

Pathological Q waves were found in 78 patients: 66 males aged (mean  $\pm$  SD)  $48.1 \pm 17.7$  years and 12 females aged  $48.8 \pm 10.7$  years (Table 1). Of these patients 54 (69%) had CAD, 7 had at least 75% stenosis in three vessels, 20 had 75% stenosis in two, and 27 had 75% stenosis in one vessel.

A significant improvement in predictive value was obtained by excluding patients with left ventricular hypertrophy, intraventricular, incomplete LBBB and RBBB (Table 1). Fourteen (43.8%) of 32 patients with these findings in the ECG had CAD compared to 40 (87%) of 46 patients without these changes ( $p < 0.0005$ ).

According to the Minnesota code the most pronounced Q waves are coded as 1, 1; less pronounced Q waves as 1, 2; and the least pronounced Q waves

**Abbreviations:** CAD = coronary artery disease; ECG = electrocardiogram; BBB = bundle branch block; LBBB = left BBB; RBBB = right BBB.

Table I Prevalence of pathological Q waves and CAD in 234 consecutive coronary arteriographies

	No. of pats		Total
	Without CAD	With CAD	
Minnesota Q code			
1 1	6	24	30
1 2	13	21	34
1 3	5	9	14
LBBB	8	1	9
No Q code	102	45	147
Total	134	100	234

as 1 3. Among the 46 patients no significant differences in prevalence of CAD were found between patients coded as 1 1 ( $n=16$ , 1 without CAD), 1 2 ( $n=23$ , 4 without CAD) or 1 3 ( $n=7$ , 1 without CAD). In the group of 46 patients 2 had significant mitral valve incompetence, probably because of papillary muscle rupture after myocardial infarction, 4 had aortic stenosis and/or incompetence and one hypertrophic obstructive cardiomyopathy with mitral incompetence. 6 of these 7 patients had CAD. Thirty-five of the 46 patients had angina pectoris and 34 of these 35 patients had CAD while 6 of 11 patients without angina pectoris had CAD ( $p<0.01$ ).

The Minnesota code Q/RS criteria fulfilled by the 46 patients were as follows (figures in parentheses indicate number of patients with CAD): 1) Q/R amplitude ratio 1/5 or more plus Q duration of at least 0.02 sec in any of leads I, II,  $V_{2-6}$ ,  $n=14$  ( $n=13$ ); 2) Q duration of at least 0.03 sec in any of leads I, II,  $V_{2-6}$ ,  $n=3$  ( $n=2$ ); 3) QS patterns in each of leads  $V_1$  and  $V_2$ ,  $n=9$  ( $n=7$ ); 4) Q duration of at least 0.03 sec in lead III plus any Q wave of at least 0.1 mV in aVF,  $n=14$  ( $n=12$ ); 5) Q duration of at least 0.03 sec and R wave of at least 0.3 mV in aVL,  $n=2$  ( $n=2$ ); 6) R wave decreasing to 0.2 mV or less or QS pattern when R wave is present in adjacent leads to the right of the chest,  $V_{2-6}$ ,  $n=4$  ( $n=4$ ).

## DISCUSSION

Description of the relationship between myocardial infarction, CAD and pathological Q waves is based on patho-anatomical studies (14, 15, 16). Myers pointed out already in 1950 that ventricular hypertrophy (12) and BBB (13) were associated with pathological Q waves although myocardial infarction

could not be demonstrated at autopsy. The introduction of selective coronary arteriography and left ventricular angiography has demonstrated that in patients with CAD without left ventricular hypertrophy, LBBB or left hemiblock accurately predicted the presence and left ventricular dyssynergy (11). Also in patients with previous myocardial infarction Q waves are perfect indicators of left ventricular hypertrophy (6). We found that pathological Q waves were an erroneous diagnosis of ischemic heart disease in patients with hypertrophic obstructive cardiomyopathy (7). Gau et al. (4) also found that pathological Q waves misleading in relation to CAD in 6 of 10 patients with congestive and in 11 of 11 obstructive cardiomyopathy. At least some patients had left anterior hemiblock which was shown by Farnham and Shah (3) to be an anteroseptal myocardial infarction. Hjalmarsson (8) found near normal coronary arteries in patients with pathological Q waves and left ventricular hypertrophy. No information was available about axis deviation, intraventricular conduction disturbances or the number of patients with left hemiblock seen on the illustrations. Farnham (2) investigated 50 patients with ECG evidence of inferior transmural myocardial infarction using the same criteria as we did. They found 10% CAD in the right coronary artery in 43 patients and 7% in the left anterior descending artery in 47 patients. Excluding patients with left ventricular hypertrophy, BBB and aortic valve disease, Farnham (10) found CAD in 47 of 50 patients with pathological Q waves. CAD was found in 14% of 162 patients with codable Q waves by Farnham.

Table II Prevalence of CAD in 78 patients with pathological Q waves in relation to left ventricular hypertrophy, ventricular conduction disturbances and left axis deviation

	No. of patients Without CAD
Left ventricular hypertrophy	7
Intraventricular block	2
RBBB	6
Incomplete LBBB	1
Left axis deviation	2
No conduction disturbances	
Left ventricular hypertrophy or left axis deviation	6

Ich et al found CAD in 35 (76%) of 46 (20) and in 103 (94%) of 109 men (21) below of age with pathological Q waves. The number of patients with CAD thus varied from 40%. It depends on patient selection in with increasing proportion of patients with ectons and decreases with increasing proportion of patients with hypertension valvular disease and cardiomyopathy. In most reports concerning Q waves and CAD specific information about hypertrophy QRS axis and/or

study shows that pathological Q waves are predictors of coronary artery disease especially in patients with left ventricular hypertrophy and deviation QRS duration of at least 0.12 s. Incomplete LBBB in the ECG. The predictive value is further increased by adding information about angina pectoris. It should be stressed that we found no difference in the predictive value of different types of coded Q waves.

#### ACKNOWLEDGEMENTS

Our study was supported by grants from the Danish Research Foundation and the Danish Heart Association.

#### REFERENCES

1. M D McAllister H A & de Castro C Myocardial infarction without atherosclerosis *Am J Med* 231 951 1975
2. E M Coqui S Greenberg H & Pink B H Inferior myocardial infarction and right coronary artery occlusive disease *Br Heart J* 37 464
3. Shah D J & Shah P M Left anterior block simulating anteroseptal myocardial infarction *Am Heart J* 92 363 1976
4. G T Goodwin J F Oakley C M Olsen E I Rahumtoola S H Raphael M J & Steiner E Q waves and coronary arteriography in cardiomyopathy *Br Heart J* 34 1034 1972
5. Hansen J Fischer Selective coronary arteriography *Judkins Dan Med Bull* 25 63 1978
6. Coronary arteriographic findings in patients with

- previous acute myocardial infarction *Acta Med Scand* 204 397 1978
7. Hansen J Fischer Pedersen Bjergaard O Stage P & Efsen F Idiopathic hypertrophic subaortic stenosis *Acta Med Scand* 197 249 1975
8. Hilsenrath J Hamby R I Glassmann E & Hoffmann I Pitfalls in prediction of coronary arterial obstruction from patterns of anterior infarction on electrocardiogram and vectorcardiogram *Am J Cardiol* 29 164 1972
9. Judkins M P Percutaneous transfemoral selective coronary arteriography *Radiol Clin North Am* 6 467 1968
10. Lee G B Wilson W J Amplatz K & Tuna N Correlation of vectorcardiogram and electrocardiogram with coronary arteriogram *Circulation* 38 189 1968
11. Miller R R Amsterdam E A Bogren H G Massumi R A Zelis R & Mason D T Electrocardiographic and cineangiographic correlations in assessment of the location nature and extent of abnormal left ventricular segmental contraction in coronary artery disease *Circulation* 49 447 1974
12. Myers G B QRS-T patterns in multiple precordial leads that may be mistaken for myocardial infarction I Left ventricular hypertrophy and dilatation *Circulation* 1 844 1950
13. — QRS-T patterns in multiple precordial leads that may be mistaken for myocardial infarction III Bundle branch block *Circulation* 2 60 1950
14. Myers G B Klein H A & Huratzka T II Correlation of electrocardiographic and pathologic findings in large anterolateral infarcts *Am Heart J* 36 838 1948
15. — V Correlation of electrocardiographic and pathologic findings in posterior infarction *Am Heart J* 38 547 1949
16. Myers G B Klein H A & Stoffer B F I Correlation of electrocardiographic and pathologic findings in anteroseptal myocardial infarction *Am Heart J* 36 535 1948
17. Rios J C Sinderson T & Goldberg S Electrocardiographic-angiographic correlations in coronary heart disease *Cardiovasc Clin* 8 111 1977
18. Rose G A & Blackburn H Cardiovascular survey methods WHO Geneva 1968
19. Rosenbaum M B Elizari M V & Lazzari J O The hemiblocks Tampa Tracings Oldsmar 1970
20. Welch C C Proudfit W L & Sheldon W C Coronary arteriographic findings in 1000 women under age 50 *Am J Cardiol* 35 211 1975
21. Welch C C Proudfit W L Sones F M Shirey E K Sheldon W C & Razavi M Cinecoronary arteriography in young men *Circulation* 42 647 1970



# Familial Occurrence of Intracranial Aneurysms

Lars Stavenow

From the Department of Medicine Malmö General Hospital Malmö Sweden

**ACT** Intracranial aneurysms occurring in families are reported. As a result of the discovery of splenic artery aneurysms in one of the families the relation between intracranial aneurysms and aneurysms in other sites is discussed. It is stressed forward that aneurysms might be a part of a generalized connective tissue disease, and the relation between aneurysms and some connective tissue diseases is stressed. At present extensive angiographic examinations in family cases cannot be recommended in every family.

**Key words:** cerebral aneurysms, splenic artery aneurysms, fibromuscular hyperplasia, connective tissue diseases.

Acta Med Scand 206 197-1979

The familial occurrence of intracranial aneurysms is rare. In 1977 there were only 47 such families in Sweden. Approximately 100 cases described in the literature (7). Many authors have speculated about the prevalence and the genetic pattern of familial occurrence of aneurysms, but to clarify the picture additional cases are reported. Between 1970 and 1976 90 cases of subarachnoid haemorrhage were diagnosed at our department. In these cases a ruptured intracranial aneurysm was documented. Three families including more than one member with intracranial aneurysms were found among these cases. The three families will be described here.

## CASE REPORTS

Family I (Fig 1)

Female, born in 1935 (no. 19 in Fig 1). She was admitted to hospital because of hypertension. Her family included several members with strokes. She had been troubled by headache for some years and had undergone two operations for varicose veins. She had been treated with L-thyroxin for an atoxic goitre. Examination of the blood pressure without treatment 90/115. She had a slight thyroid enlargement and a synchronous bruit was heard just left of the neck.

Because of her remarkable family history and her own strong wish to know whether she had the same findings as her brother and daughter (vide infra) a cerebral angiography was carried out. No aneurysms were demonstrated. A selective renal angiography also revealed normal findings. Because of the bruit recorded at the examination an abdominal angiography was carried out. Three aneurysms 3-4 mm in size were found in the branches of the splenic artery just near the splenic hilus (Fig 2).

An operation on these aneurysms was not regarded necessary for the moment. The blood pressure was satisfactorily controlled with propranolol and bethandine.

She came to the hospital 15 months later because of abdominal pains. The bruit from the splenic artery aneurysms was no longer demonstrable, possibly because of thrombotisation of the aneurysms. The pains disappeared and no new abdominal angiography was carried out.

**Case B.** The brother of case A (no. 16 in Fig 1). He died 36 years old of subarachnoid haemorrhage due to a ruptured aneurysm on the left middle cerebral artery, documented at autopsy.

**Case C.** The daughter of case A (no. 27). She died 77 years old of subarachnoid haemorrhage due to a ruptured aneurysm on the left internal carotid artery. The rupture occurred 7 months after a normal delivery.

In addition to these three cases with documented aneurysms there were three other family members with conceivable intracranial aneurysms.

The mother of case A (no. 11) died suddenly 54 years old and her death certificate read: Malignant hypertension + cerebral haemorrhage. Autopsy was not performed.

The aunt of case A (no. 4) died 51 years old. Her death certificate read: Cerebral haemorrhage. She was paralysed 6 months before she died. Autopsy was not performed.

The uncle of case A (no. 5) died suddenly 61 years old. He fell down from a ladder and had just before complained of headache. Autopsy was not performed.

## Family II

**Case D.** Female, aged 57. She had suffered from a mild hypertension for some years. In 1972 she got a subarachnoid haemorrhage and an aneurysm on the left middle cerebral artery was ligated with satisfactory result.

**Case E.** The brother of case D. At the age of 60 he suddenly lost consciousness and bilateral carotid angiography demonstrated an aneurysm on the anterior communicating artery. Hypotensive treatment with a



Case I

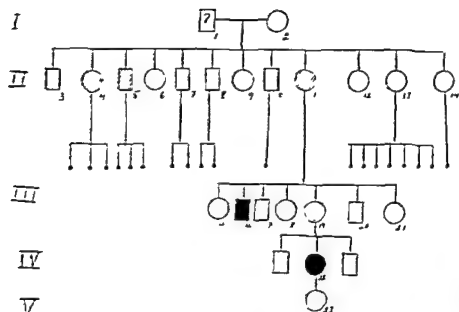


Fig 1 Family relations and the relations of the aneurysms. ■ = Documented aneurysms, ○ = intracranial aneurysms, □ = splenic artery aneurysms. Circles indicate intracranial aneurysms, rectangles indicate splenic artery aneurysms.

methylglutamate and thiazide diuretic was started. An angiography three months after the rupture showed that the aneurysm had declined in size.

### Family III

**Case F** Male, aged 49, with a high consumption of alcohol for several years suddenly experienced weakness in the limbs and his condition worsened on the following day. A cerebral angiography demonstrated an aneurysm on the left internal carotid artery just at the beginning of

the posterior cerebral artery. The aneurysm was treated by ligature and the patient has been well since the exception of dizziness.

**Case G** The sister of case F. She had been healthy since her last pregnancy at the age of 28. At the age of 33 she got a left facial palsy and headache. An angiography showed a narrow portion of the cerebral artery which was interpreted as an aneurysm. At the age of 33 she again experienced sudden headache and left facial palsy and aphasia. A new angiography



Fig 2 Abdominal angiography from case showing three distinct aneurysms (arrows).

rowing of the right middle cerebral artery. In young years she suffered from attacks of headache, blindness, loss of memory and sometimes weakness of the left extremities. At 36 years of age, during an operation, she developed a complete left paralysis and died soon thereafter.

A haematoma in the right hemisphere reaching the ventricles was found at autopsy. The cerebral arteries showed only a very slight degree of arteriosclerosis. On the other hand, a small aneurysm was demonstrated on the right middle cerebral artery. Repeated from this aneurysm with consecutive arterial thrombosis might possibly have been mistaken for thrombotic angiographies.

## DISCUSSION

Arterial aneurysms are regarded as congenital in many cases, and by studying the familial cases one can get an idea of the significance of the factors. The exact prevalence, however, is determined only by extensive angiographic studies of the affected families. The real prevalence is probably far more frequent than indicated by the literature, because some family members have asymptomatic aneurysms, or intracranial aneurysms may be overlooked at autopsy of patients dying from other causes. Aneurysms in the familial cases tend to rupture at a younger age than in the non-familial cases. Furthermore, the occurrence of aneurysms at identical sites in two relatives is more than twice as frequent (7).

The exact role and nature of genetic factors in the familial cases is not known. As Bannerman et al. (1) point out, it is probably a very heterogeneous condition in which genetic factors, fortuitous factors, aggregation and the relation to known systemic diseases such as Ehlers-Danlos syndrome may play a part. Intracranial aneurysms may be related to different conditions, especially those involving the connective tissue, such as Ehlers-Danlos syndrome, polycystic degeneration, angiodysplasia, coarctation of the aorta, Marfan's syndrome and fibromuscular hyperplasia (FMH) of the arteries. The association between intracranial aneurysms and aneurysms in other sites is not a frequently reported phenomenon. Intracranial aneurysms are most commonly associated with renal aneurysms (2, 10, 11, 12, 17). They can also occur together with FMH in renal arteries (2, 6, 13). Other associations are known.

The aetiology of cerebral aneurysms is usually congenital defects in the arterial wall. Other aneurysms that may have a congenital aetiology include renal, splenic, hepatic and coeliac artery aneurysms (3, 15). Aneurysms on the superior mesenteric artery and its branches, however, are regarded as mycotic in origin in most cases (5), and aneurysms on the femoral and popliteal arteries almost exclusively have an arteriosclerotic genesis (5).

With this background, it is concluded that congenital aneurysms, just like FMH, sometimes must be regarded as a generalized condition of connective tissue. Perhaps one should include some other connective tissue diseases and talk about a special defective connective tissue syndrome. Patient A developed splenic artery aneurysms while two of her relatives suffered from intracranial aneurysms. Probably there exists a hereditary disposition for weaknesses in the arterial wall. In what arteries these weaknesses contribute to the development of aneurysms may be dependent on difference in histological structure, local haemodynamic or fortuitous factors.

An entity with great similarity to arterial aneurysms is FMH. This condition, though most common in the renal arteries, is a generalized condition of small and medium sized arteries. Besides the renal arteries, FMH may also engage the splenic artery, the coeliac artery, the carotid and vertebral arteries, the mesenteric arteries and the iliac arteries (2, 4, 6, 19). As mentioned before, FMH may be associated with intracranial aneurysms (6, 13, 19). Familial occurrence of FMH has been described (16). Wylie et al. (19) discuss whether there exists a common aetiology for FMH and intracranial aneurysms. The most convincing evidence is their histological similarity.

Jain (8) suggests that all members of a family in which more than one member has intracranial aneurysms should be investigated. He also concludes that cerebral angiography should be considered in closely related patients with polycystic kidneys, Ehlers-Danlos syndrome and other similar conditions. He also reports successful surgical treatment of incidentally discovered non-ruptured aneurysms (9). Taking into account the relative rarity of the condition and the risk of radiological and operative procedures, it is doubtful whether cerebral angiography is indeed indicated in all these cases. Angiography of all members of a

large family (like family I presented here) leads to problems sometimes of a far reaching psychological nature. One possibility is to direct the investigations towards members showing certain risk factors for example hypertension.

No strict recommendations for the investigation in these cases can be given today—it is advisable to know more about the prevalence first and also to have a very deep insight into the families concerned especially from a psychological viewpoint. It is also important to establish firm collaboration with a neurosurgical department and to be familiar with the neurosurgeons attitude to prophylactic surgical treatment before entering upon extensive family studies.

## REFERENCES

- Bannerman R M, Ingall G B & Graf C J. The familial occurrence of intracranial aneurysms. *Neurology* 20: 783, 1970.
- Belber C J & Hoffman R B. The syndrome of intracranial aneurysms associated with fibromuscular hyperplasia of the renal arteries. *J Neurosurg* 28: 556, 1968.
- Engelbrecht H E. Renal artery aneurysms. Case report and review. *S Afr Med J* 42: 1044, 1968.
- Ennis J T & Bateson E M. Fibromuscular dysplasia of the internal carotid arteries—a report of 3 cases. *Br J Radiol* 43: 457, 1970.
- Friedman S A. The diagnosis and management of arterial aneurysms. *Med Clin North Am* 57: 1525, 1973.
- Handa J, Kamijyo Y & Handa H. Intracranial aneurysms associated with fibromuscular hyperplasia of renal and internal carotid arteries. *Br J Radiol* 43: 483, 1970.
- Hashimoto I. Familial intracranial; cerebral vascular anomalies. *J Neurol* 1977.
- Jan K K. Familial intracranial aneurysms. *Neurosurgery* 30: 179, 1974.
- Surgery of intact intracranial aneurysms. *Neurosurg* 40: 495, 1974.
- Jones E L & Finney G G. Aneurysms. *Arch Surg* 97: 640, 1968.
- Nevins S & Williams D. The polybag aneurysms. *Lancet* 2: 955, 1937.
- Owens J C & Coffey R J. An aneurysm of the splenic artery including a report of 62 cases. *Int Abstr Surg* 97: 313, 1953.
- Russo L. Fibromuscular hyperplasia of the arteries. Report of a case associated with aneurysms and skeletal deformities of the literature. *Mt Sinai J Med NY* 1968.
- Sheps S G, Spittell J A, Farberwalds J E. Aneurysms of the spleen: special reference to bland aneurysms. *Am J Surg* 33: 381, 1959.
- Stanley J C, Thompson N W. Splanchic artery aneurysms. *Arch Surg* 1970.
- Stavenow L, Henriques B, Elbert S E & Hood B. Combination of hyperplasia, renal aplasia, hypoplasia and otosclerosis occurring in the same family. *Acta Med Scand* 1968.
- Vaughan T C, Barry W F, Jelks J, Johnsrude I S. Renal artery aneurysms in hypertension. *Radiology* 99: 787, 1971.
- Wu W Q. Coexistent carotid and renal artery aneurysms. *Surg Neurol* 1: 351, 1973.
- Wyle E J, Binkley F M & Patek D J. Extrarenal fibromuscular hyperplasia. *Am J Surg* 111: 149, 1966.

## Alkaline Phosphatase in Women with Osteoporosis

A G Hulth B E Nilsson N E Westlin and P E Wiklund

From the Department of Orthopedic Surgery, Malmö General Hospital  
University of Lund, Malmö, Sweden

**ACT** Altogether 15 partially independent measurements of bone mass in 100 women with clinical and roentgenological signs of osteoporosis were related to the alkaline phosphatase activities of the individuals. There was a slight but significant correlation indicating an increasing alkaline phosphatase activity with decreasing bone mass. This relation was not caused by interaction of age. There was no correlation between alkaline phosphatase activity and clinical or morphological signs of osteoporosis. The changes could not be explained by age. It is suggested that a slight increase in the alkaline phosphatase activity in women with a more severe osteoporosis is related to bone resorption.

**Key words:** alkaline phosphatase, osteomalacia, osteoporosis.

Acta Med Scand 206 201 1979

Alkaline phosphatase is frequently used in clinical diagnostic work as a screening test of disease, mainly for the disclosure of osteoporosis or for studies on the consequences for the metabolism of renal disease and hemodialysis. The purpose of this study was to relate this variable alkaline phosphatase to parameters of bone mass and composition in a series of women with clinical signs of osteoporosis.

## SELECTION OF PATIENTS

For the study were selected 100 women who had sought medical advice because of back ache and who had clinical evidence of spinal osteoporosis. Clinically there was a large variation with cases ranging from doubtful radiological to severe osteoporosis with deformity of the vertebral column and multiple fractures. The women were all postmenopausal, their age at the time of the examination was  $63.3 \pm 7.6$  years. Their menopausal age was  $46.7 \pm 4.5$  (mean  $\pm$  S.D.).

## METHODS

*Alkaline phosphatase*

The alkaline phosphatase was estimated by a modified Busch and Busch method using gamma-amino-methyl propanol buffer, para-nitro-phenyl phosphate as substrate and magnesium as activator with an optimal pH of 10.8. With this method the normal variation in adults is  $\sim 8$  units with a 95% confidence limits.

*Spinal osteoporosis*

Radiological density was classified 0-4 with increasing severity of radiological osteoporosis visible on lateral radiograms of the lumbar spine (11).

The number of crush fractures 0-5 or more was determined from lateral radiograms of the thoracic and lumbar spine.

The vertebral ratio was calculated as the ratio between the central height and the sagittal diameter of the body of the lumbar vertebra located most closely to the central beam in lateral radiograms of the lumbar spine. Only in 73 cases the radiograms were of sufficient quality for this measurement.

The spinal ratio is defined as the ratio between the height of the head plus trunk measured in sitting position and the total height. This variable is a parameter of spinal shortening (8).

*Iliac crest biopsy*

A  $0.5 \times 1.5$  centimeter cylindrical bone sample was obtained from the left iliac crest by the method of Burkhardt (2). The undecalcified sample was imbedded in methylmethacrylate, sectioned and stained by a modified Goldner technique. The surface and the volume of bone and osteoid in the sections were estimated using a point and wave pattern engraved on the eye piece of the microscope (6). Also the osteoid was calculated and expressed as % of total bone. Sixty-four biopsies of sufficient quality to be included were obtained.

*Gamma absorptiometry*

The bone mass in the forearm was measured by a photon absorptiometer technique (7). The method is similar to that of Cameron and Sorenson (3). The main difference being the source of radiation americium  $^{241}$  instead of cadmium  $^{109}$ . The bone mass was measured in 6 centimeters proximally of the dorsal distal edge of the ulna.

Table I *The relationship between alkaline phosphatase and parameters of bone mass*

Variable	No	r	p
Spine			
Radiological density	99	0.21	$0.05 < p < 0.02$
Crush fractures	98	0.15	$p > 0.1$
Vertebral ratio	73	-0.10	$p > 0.1$
Spinal ratio	87	-0.12	$p > 0.1$
Iliac crest			
Bone surface	64	-0.26	$0.05 > p > 0.02$
Bone volume	64	-0.17	$p < 0.1$
Forearm			
Left 1 cm	93	-0.33	$0.01 < p < 0.001$
Right 1 cm	96	-0.24	$0.02 < p < 0.01$
Left 6 cm	94	-0.25	$0.02 < p < 0.01$
Right 6 cm	90	-0.33	$0.01 < p < 0.001$
Metacarpus			
Left	97	-0.22	$0.05 < p < 0.02$
Right	97	-0.17	$0.1 < p < 0.05$
Femur			
Left	99	-0.22	$0.05 < p < 0.02$
Right	99	-0.27	$0.01 < p < 0.001$
Trabecular pattern	95	-0.18	$0.1 < p < 0.05$

*Metacarpal and femoral cortices*

The cortical thickness was measured on the midshaft of the second metacarpal and the femur in anteroposterior radiograms. In both instances the combined cortical thickness was measured and corrected for the width of the bone (1, 4).

*Femur trabecular pattern*

The trabecular pattern of the proximal end of the femur was estimated on anteroposterior radiograms of the hip according to the method of Singh et al. (12). Both hips were used for the estimate.

*Statistics*

The relationship between alkaline phosphatase and the various parameters of bone mass was studied by the method of linear correlation. It should be taken into account that some of the variables (radiological density, number of crush fractures and trabecular pattern) are non parametric.

## RESULTS

The alkaline phosphatase for the entire group was  $6.7 \pm 2.0$  units. There was no correlation between age and alkaline phosphatase ( $r = 0.04$ ,  $p > 0.1$ ). In 9 out of 15 parameters of bone mass there were significant correlations indicating increasing alkaline phosphatase activity with decreasing bone mass (Table I). In some of the variables there were suggestive relationships with the same tendency in all of the correlations, significant or not; the tendency was homogeneous. (Note that radiological

density and number of crush fractures were in rank with decreasing bone mass.)

There was no correlation whatsoever between the amount of osteoid, total or relative bone mass and alkaline phosphatase (Table II).

Twelve women had alkaline phosphatase activities of 10 or more (10-14 units). They were searched for possible distinguishing features. In no case did the bone biopsy show osteoporosis. In one instance the alkaline phosphatase was measured within a few weeks after a vertebral compression fracture. The activity became normal. In another case the elevated value was recorded shortly after the bone biopsy was taken. In the remaining cases there was no clinical explanation, suggesting a close relationship in time with the bone mass. In most instances more than one value over the limits was recorded. The 12 women did not differ in age from the average of the sample nor were there any clinical features distinguishing them.

Table II *The relationship between alkaline phosphatase and osteoid*

Variable	No	r	p
Osteoid surface	64	0.00	$p > 0.1$
Osteoid volume	64	0.00	$p > 0.1$
% osteoid surface	64	0.03	$p > 0.1$
% osteoid volume	64	-0.03	$p > 0.1$

## DISCUSSION

Alkaline phosphatase activity of the women in this study was increased only slightly above the average. Only a minority of the patients had any abnormal values.

The object of the test was to identify patients with metabolic bone disease other than idiopathic osteoporosis, particularly osteomalacia. Clinically, it was not successful and the alkaline phosphatase activity was not related to the amount of tissue found in bone biopsies.

Bohman (10) and Keating et al. (5) demonstrated that alkaline phosphatase activity increased with age in healthy women. In the present study, only women with clinical osteoporosis in a more narrow age range, no such correlation could be demonstrated. Therefore, the inverse relationship between bone mass and alkaline phosphatase activity is probably not a result of interaction.

Bohman and Westlin (9) demonstrated that in women with femoral neck fracture the alkaline phosphatase activity was elevated during the first months after the injury. No such relationship with fracture could be demonstrated in the present study.

From the correlation coefficients it can be seen that there is a considerable residual variance in the alkaline phosphatase data, less than 10% of the variance is explained by correlation to bone mass. The relationship between alkaline phosphatase and bone mass found in this study has not been previously described. The reason for this relationship is not known but it is suggested that idiopathic osteoporosis is an increased alkaline phosphatase activity, a sign of increased bone resorption.

## REFERENCES

- 1 Barnett E & Nordin B E C. The radiological diagnosis of osteoporosis. A new approach. *Clin Radiol* 11: 166, 1960.
- 2 Burkhardt R. Technische Verbesserung und Anwendungsbereich der Histo-Biopsie von Knochenmark und Knochen. *Klin Wochenschr* 44: 326, 1966.
- 3 Cameron J R & Sorensson J. Measurement of bone mineral in vivo. An improved method. *Science* 142: 230, 1963.
- 4 Gam S M, Rohmann C G & Nolan P. The developmental nature of bone changes during aging (ed J E Birren). Thomas, Springfield III, 1963.
- 5 Keating Jr F R, Jones I D, Elveback L R & Randall R V. The relation of age and sex to distribution of values in healthy adults of serum calcium, inorganic phosphorus, magnesium, alkaline phosphatase, total proteins, albumin and blood urea. *J Lab Clin Med* 73: 825, 1969.
- 6 Merz W A & Schenk R K. Quantitative structural analysis of human cancellous bone. *Acta Anat (Basel)* 75: 54, 1970.
- 7 Naucler L O W, Nilsson B E & Westlin N E. An apparatus for gamma absorptiometry of bone—technical data. *Opuscula Medica Technica Lundensia* XII: 13, 1974.
- 8 Nilsson B E. Spinal osteoporosis and femoral neck fracture. *Clin Orthop* 68: 93, 1970.
- 9 Nilsson B E & Westlin N E. The plasma concentration of alkaline phosphatase, phosphorus and calcium following femoral neck fracture. *Acta Orthop Scand* 43: 504, 1972.
- 10 Roberts L B. The normal ranges with statistical analysis for seventeen blood constituents. *Clin Chim Acta* 16: 69, 1967.
- 11 Saville P D. A quantitative approach to simple radiographic diagnosis of osteoporosis. Its application to the osteoporosis of rheumatoid arthritis. *Arthritis Rheum* 10: 416, 1967.
- 12 Singh M, Nagrath A R & Mami P S. Changes in trabecular pattern of the upper end of the femur as an index of osteoporosis. *J Bone Joint Surg (Am)* 52: 457, 1970.

## ACKNOWLEDGEMENT

Financial support was obtained from the Swedish Medical Research Council (project no. B 77 17X 2737-09B).



# Bone Biopsy in Women with Spinal Osteoporosis

Anders G. Hulth, Bo E. Nilsson, Nils E. Westlin and Per Frih, Wiklund

From the Department of Orthopedic Surgery, Malmö General Hospital, University of Lund, Malmö, Sweden

CT iliac crest biopsies were obtained from 62 of whom had been clinically and radiologically classified as osteoporotics. The amount of surface was measured by a histological method. It was demonstrated that the osteoid does not differ between osteoporotic and control women and that osteomalacia in both groups.

Key words: bone biopsy, osteomalacia, osteoporosis.

Acta Med Scand 206: 205-206, 1979.

an important feature in idiopathic osteoporosis is the presence of pathological laboratory findings. Unless it may be assumed that a group of women with signs of osteoporosis such as back pain and radiological changes contains one or more in which further diagnostic work in profit. Among others, Andersson et al. (2) and Chalmers et al. (4) formulate a hypothesis according to which osteomalacia is a fairly frequent condition in elderly women. Osteomalacia is in marginal difficult diagnosis. The most reliable tool is the bone biopsy (5).

The purpose of the present study was to test the value of iliac crest biopsy for the diagnosis of osteomalacia in a group of women classified as osteoporotics.

## PATIENTS

Consecutive women were selected depending on symptoms and radiological signs of spinal osteoporosis. All patients had been first referred because of osteoporosis. On the next radiogram the diagnosis of osteoporosis was based on an obviously low radiological crush fractures or both. None of the patients had of severe dietary deficiency, malabsorption or renal disease. The alkaline phosphatase levels were normal in all.

## Controls

Iliac crest samples were obtained from 48 autopsies on women in the Department of Forensic Medicine. Included were individuals who had suffered sudden death, mostly cardiac or death by violence. Excluded were individuals who were known to be alcoholics or who had undergone gastrointestinal surgery. The age distribution of both samples is demonstrated in Fig. 1.

## METHODS

### Estimation of osteoid

The method and instrument of Burkhardt (3) were used. In local anaesthesia a small incision was made over the iliac crest and a cylindrical 0.5-1.5 cm bone sample was obtained with a motor-driven miller. This is the method to collect a sample without deforming the cancellous bone.

The undecalcified samples were embedded in methyl methacrylate and 4-6 µm sections were made in a hard section microtome. The sections were stained by a modified Goldner (6) method. In the resulting slides the osteoid tissue can be distinguished from the calcified material by colour. The surface occupied by bone and osteoid was measured by counting intersections between bone and osteoid and a wave pattern engraved on the eyepiece of the microscope (7). Only trabecular bone was evaluated. The abundance of osteoid tissue was calculated as the percentage osteoid surface of total bone surface.

## RESULTS

The per cent osteoid was  $3.2 \pm 4.0$  and  $7.7 \pm 4.0$  (average  $\pm$  S.D.) in osteoporotics and controls respectively. There was no significant difference between the groups. As indicated by the standard deviations the variable is skewedly distributed (Fig. 2). There was no correlation between age and per cent osteoid in this study.

## DISCUSSION

The skewedness of the data would imply that in osteoporotic women the bone contains no or at most no detectable osteoid whereas in some and



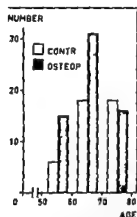


Fig 1 Age distribution of osteoporotics and controls

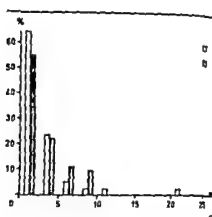


Fig 2 Distribution of osteoid in osteoporotics

viduals the amount of osteoid is slightly increased because of some skeletal disorder. However the same distribution was found in the controls. Values below 10% cannot be referred to as pathological. This should be compared with the findings of Aaron (1) who proposed that the normal upper limit for osteoid in an English population is 24% of the trabecular surface. Only in one of the 62 osteoporotics a definite increase above normal could be demonstrated. She was a woman whose symptoms did not differ from the others, nor did she have any abnormalities in serum calcium, serum phosphorus or alkaline phosphatase in repeated measurements.

Our conclusion is that bone biopsy as a routine screening method to detect osteomalacia in women with osteoporosis does not return the efforts invested. It should be limited only to patients with signs and symptoms deviating from the usual term of osteoporosis.

Most of the data indicating that osteomalacia is common in old women has been collected in Britain. Possibly nutritional habits and other ethnical particularities contribute to the discrepancies. Our observations and conclusions are therefore valid only under the present conditions in Southern Sweden.

#### ACKNOWLEDGEMENT

Financial support was obtained by the Swedish Research Council (project no B 77 17X), Greta and Johan Kock and Alfred Öndations.

#### REFERENCES

- 1 Aaron J E. In: Calcium phosphate metabolism (ed B E C Nordin) p 14. Livingstone, Edinburgh 1976.
- 2 Andersson I, Campbell A E R, Deelman B M. Osteomalacia in elderly. *Med J* 11: 429 1966.
- 3 Burkhardt R. Technische Anwendungsbereich der Histo-Biopsie und Knochen. *Klin Wochenschr* 44: 336.
- 4 Chalmers J, Conacher W D H, Goss P J. Osteomalacia—a common disorder in women. *J Bone Joint Surg (Br)* 49: 405.
- 5 Garner A & Bell J. Quantitative of mineralized and unmineralized bone in azotaemia and intestinal malabsorption. *Pathol* 91: 543 1966.
- 6 Goldner J. A modification of the Masson technique for routine laboratory purposes. *J Clin Pathol* 14: 237 1938.
- 7 Merz W A & Schenk R A. Quantitative analysis of human cancellous bone. *J Bone Miner Res* (Basel) 75: 54 1970.

# Erythrocyte Sedimentation Rate in a Population Sample of Women with Special Reference to its Clinical and Prognostic Significance

Vilhjalmur Rafnsson Calle Bengtsson Jan Lennartsson Olof Lindquist  
Henry Noppa and Elisabeth Tibblin

*From the Departments of Medicine II and Clinical Chemistry Sahlgrenska Sjukhuset  
University of Göteborg Göteborg Sweden*

**CT** A comprehensive population study of aged 38-60 was carried out in Göteborg, 1968-69. The same women were re-studied later, in 1974-75. Erythrocyte sedimentation rate (ESR) was studied on both occasions. A highly significant rise in ESR with age was noted cross-sectionally and longitudinally, which at the increase was related to age and was not effect. The mean annual increase in ESR was 0.6 mm/h, but there was a significant difference between the ages studied, the increment being higher in the upper age groups. Women with ESR  $\geq 30$  mm/h (here defined as ESR  $\geq 30$  mm/h) had lower Hct values than other women. Leucocyte counts were higher in women with ESR  $\geq 30$  mm/h than the others, but differences were statistically significant only in the upper age groups. Serum iron levels were lower in women with high ESR, while albumin levels were similar to those in the other women. Significant differences were found for transferrin saturation (lower in women with high ESR). Triglyceride levels were similar, while triglyceride levels tended to be or were significantly higher in women with high ESR. About half of the women with ESR  $\geq 30$  mm/h had a possible explanation for raised ESR. In no case did an increased ESR lead to a new diagnosis of clinical significance, either in 1968-69 or in 1974-75. Nor had any been missed in women with a high ESR in 1968, according to the re-examination six years later. Except one woman, in whom the diagnosis of neoplastic disease was made in the interval between the two examinations, had ESR  $\leq 30$  mm/h in 1968 and women in whom a neoplastic disease had later had on average no higher ESR than the others. It is concluded that for prognostic purposes, ESR is of very limited value.

Erythrocytes separate from plasma at a variable rate which may be elevated or depressed in connection with disease. The erythrocyte sedimentation rate (ESR) has been put to wide clinical use since the works of Fåhræus (7) and Westergren (20) but its clinical significance has been poorly evaluated. ESR may be elevated in apparently healthy individuals. The reason for the association between various physiological and pathological conditions and raised ESR is not understood in detail but has been attributed to changed properties of the plasma.

The main purpose of the present study on ESR was to increase our knowledge of its clinical significance and the aims of this paper are to study 1) the distribution of ESR values in a female population with special reference to differences with age 2) other concomitant laboratory changes in the blood of women with raised ESR 3) the causes of raised ESR in a defined population 4) the prognosis of subjects with raised ESR.

## STUDY POPULATION

A population study of women in Göteborg, Sweden, was performed in 1968-69 (1). Altogether 1462 women in the age strata 38, 46, 50, 54 and 60 years were examined. They were representative of the total population of women in Göteborg in the ages studied. The sample was obtained from the Revenue Office Register. The same women were re-examined six years later in 1974-75 when they were aged 44, 52, 56, 60 and 66. The two studies were performed in a similar way (2). Numbers of participants and participation rates in the two studies are shown in Table I.

## METHODS

Both studies were carried out during a one year period. A date for an examination was settled. For menstruating

erythrocyte sedimentation rate age changes in disease population study women  
Acta Med Scand 206 207 1979

Table III ESR in relation to age and intraindividual differences in women who participated in both studies with statistical significance of intraindividual differences

n	1968-69			1974-75			Difference		p
	Age (y)	ESR (mm/h)		Age (y)	ESR (mm/h)		Mean	S D	
		Mean	S D		Mean	S D			
333	38	10.8	11.3	44	12.7	12.5	1.9	11.5	<0.01
385	46	11.0	8.4	52	14.9	11.6	3.9	10.2	<0.001
349	50	11.8	7.7	56	16.6	13.2	4.9	11.8	<0.001
163	54	14.2	10.3	60	18.2	13.2	4.0	11.9	<0.001
65	60	18.5	14.3	66	24.1	20.2	5.6	13.4	<0.01
1295		12.0	9.8		15.7	13.2	3.8	11.4	<0.001

### Women with high ESR

**Other laboratory characteristics** Women with high ESR ( $\geq 30$  mm/h) in 1968-69 were compared with the other women in each age stratum with regard to various laboratory examinations. Their Hb concentration, Hct, leucocyte count, serum iron, TIBC, transferrin saturation, serum cholesterol and serum triglyceride values are shown in Table IV. The Hb and Hct concentrations were lower in the women with high ESR. The differences are statistically significant in all the age strata studied. The leucocyte counts were higher in the women with elevated ESR, but the differences are statistically significant only in those aged 54 and 60. Serum iron levels were lower in women with high ESR (statistically significant differences in all age strata) while TIBC was similar (the only statistically significant difference being for women aged 54). Significant differences were found in all age strata for transferrin saturation. No significant differences were found for cholesterol levels. Triglyceride levels were somewhat higher in women with high ESR, but the difference is statistically significant only for women aged 54 and the total sample.

**Possible explanation** In the study performed in 1968-69 altogether 78 women had an ESR  $\geq 30$  mm/h. Possible causes of the elevated rate were found in 36 rheumatoid arthritis, 9 arthritic symptoms, 8 systemic lupus erythematosus, 2 other collagenosis, 1 chronic alcoholism, 1 severe anaemia (Hb <100 g/l), 2 uraemia, 2 pregnancy, 1 cancer, 1 ulcer cruris, 1 urinary tract infection, 2 chronic bronchitis, 4 chronic osteomyelitis, 1 Salmonella infection. The ESRs of the 42 women with no explanation for their raised values were 30-34 mm/h in 20, 35-39 mm/h in 16 and  $\geq 40$  mm/h in 7. All

these women were symptom free and felt well at the time of the study.

Of the 141 women with ESR  $\geq 30$  mm/h in 1974-75, 76 had a possible explanation for the elevated rate: rheumatoid arthritis 16, arthritic symptoms 28, systemic lupus erythematosus 1, collagenosis 1, other collagenosis 1, liver cirrhosis 1, hyperlipidaemia 3, urinary tract infection 1, pyelonephritis 7, uraemia 2, cancer 1, psoriasis 1, ulcer cruris 2, gangrene 1, bronchitis 5, other infection of the respiratory tract 3, thyroiditis 1. No apparent cause of the elevated ESR was found in 65 women. All were symptom free and felt well. Their mean ESR was 38 mm/h (S D 10.1) compared to 45.8 mm/h (S D 13.2) in the 76 women with a possible cause of the elevated ESR.

**Prognosis** Of the 1462 women who participated in both studies, 27 died during the six years between the two studies. 4 (5.2%) of those with ESR  $\geq 30$  mm/h and 23 (1.8%) of those with ESR <30 mm/h. The difference is not statistically significant. The causes of death in three of the women with ESR  $\geq 30$  mm/h were valvular heart disease, heart insufficiency, cancer of the breast, metastases and diabetes with renal complications. All these diagnoses were known before the first study (Table V). The fourth woman drowned.

Six of the women who had a possible explanation for an increased ESR in 1968-69 did not participate in 1974-75, in addition to the three who died. No new diagnosis during the period between the two studies was recorded in the 21 women with ESR  $\geq 30$  mm/h in 1968-69 who participated in 1974-75. Twenty of these women had ESR  $\geq 30$  mm/h and seven <30 mm/h when examined in 1974-75.

Comparison between women with ESR  $\geq 30$  and  $< 30$  mm/h in 1968-69

SR <30 mm/h		ESR ≥30 mm/h		p	Age (y)	ESR <30 mm/h		ESR ≥30 mm/h		p					
Mean	S D	n	Mean			S D	n	Mean	S D		n	Mean	S D		
bun concentration (g/l)															
36	135	10	15	129	10	<0.05	38	355	62.1	10.8	15	62.8	11.2	NS	
13	136	11	18	130	11	<0.05	46	412	62.3	9.7	18	63.0	9.9	NS	
33	138	10	15	124	23	<0.001	50	383	61.7	9.0	15	60.1	9.9	NS	
52	139	9	18	132	12	<0.05	54	160	60.8	8.6	18	55.4	6.5	<0.05	
59	139	8	12	130	6	<0.001	60	69	60.5	9.5	12	58.9	9.4	NS	
13	137	10	78	129	14	<0.001	Total	1379	61.7	9.7	78	60.1	9.9	NS	
rit (%)															
55	39.1	2.4	15	37.7	2.5	<0.05	38	355	31.5	14.2	15	22.1	7.3	<0.05	
39	39.6	2.8	18	38.0	1.9	<0.05	46	412	30.4	14.3	18	21.2	13.0	<0.05	
83	39.6	2.7	15	36.1	5.5	<0.001	50	383	31.2	12.5	15	22.4	10.2	<0.05	
52	40.1	2.6	18	38.5	2.7	<0.05	54	160	34.0	11.9	18	27.6	11.1	<0.05	
58	40.6	2.4	12	38.9	2.1	<0.05	60	69	34.2	9.5	12	24.2	8.5	<0.05	
76	39.7	2.7	78	37.8	3.4	<0.001	Total	1379	31.5	13.3	78	23.5	10.2	<0.001	
s (10 <sup>3</sup> l)															
47	5.54	1.76	15	5.85	2.44	NS	38	355	6.3	0.9	15	6.2	1.1	NS	
01	5.49	1.68	18	6.03	1.73	NS	46	412	6.8	1.4	17	7.0	1.5	NS	
80	5.30	1.59	15	5.89	1.87	NS	50	383	7.2	1.1	15	7.2	1.3	NS	
67	4.94	1.46	18	6.68	2.11	<0.001	54	160	7.3	1.1	18	7.7	1.3	NS	
68	5.02	1.41	12	6.05	2.50	<0.05	60	68	7.4	0.9	12	7.3	1.0	NS	
59	5.36	1.65	78	6.12	2.15	<0.001	Total	1379	6.8	1.2	77	7.1	1.3	NS	
n (μmol/l)															
55	19.0	8.1	15	13.3	3.4	<0.05	38	355	1.1	0.4	15	1.3	0.7	NS	
12	18.1	8.1	18	12.5	7.2	<0.05	46	412	1.2	0.7	18	1.4	0.6	NS	
83	18.6	7.0	15	12.9	6.1	<0.05	50	383	1.3	0.6	15	1.5	0.4	NS	
60	20.2	6.8	18	15.0	5.3	<0.001	54	160	1.4	0.7	18	1.7	0.8	<0.05	
69	20.2	5.3	12	13.8	3.8	<0.001	60	69	1.4	0.6	12	1.1	0.3	NS	
79	18.8	7.5	78	13.4	5.6	<0.001	Total	1379	1.2	0.6	78	1.4	0.6	<0.05	
Triglycerides (mmol/l)															
38	355	1.1	0.4	15	1.3	0.7	NS	38	355	1.1	0.4	15	1.3	0.7	NS
46	412	1.2	0.7	18	1.4	0.6	NS	46	412	1.2	0.7	18	1.4	0.6	NS
50	383	1.3	0.6	15	1.5	0.4	NS	50	383	1.3	0.6	15	1.5	0.4	NS
54	160	1.4	0.7	18	1.7	0.8	<0.05	54	160	1.4	0.7	18	1.7	0.8	<0.05
60	69	1.4	0.6	12	1.1	0.3	NS	60	69	1.4	0.6	12	1.1	0.3	NS
Total	1379	1.2	0.6	78	1.4	0.6	<0.05	Total	1379	1.2	0.6	78	1.4	0.6	<0.05

of the 42 women with no explanation for an d ESR in 1968-69 did not participate in in addition to one woman who had died he non participants had moved abroad and contacted the other two related at a tele interview that they had arthritic symptoms : not on treatment

n of the participants still had ESR  $\geq 30$  /hen studied in 1974-75 no definite new s was recorded. An elevation of serum ing the six year interval between the two ould possibly explain the raised ESR in one Among the 23 women without an explana their raised ESR in 1968-69 and an ESR h in 1974-75 (Table V) new diagnoses in six liver cirrhosis chronic ic leukaemia arthritis myocardial infarc one case each and hyperlipidaemia in two

**Incidence of malignant tumours** Except for one woman in whom the diagnosis of leukaemia was made later none of those who had ESR  $\geq 30$  mm/h in 1968-69 was in 1974-75 known or found to have neoplastic disease which had not been known in 1968-69. It is noteworthy that the woman with leukaemia had a normal leucocyte count in 1968-69 and an ESR  $< 30$  mm/h in 1974-75 although she had not been treated.

Table VI shows the ESR in 1968-69 of women in whom breast cancer or gynaecological cancer was detected between the two studies and who attended the study in 1974-75. None of them had ESR  $\geq 30$  mm/h in 1968-69. Mean ESR in 1968-69 of ten women with breast cancer was 9.8 mm/h (S D 6.4) and of nine with gynaecological cancer 10.8 mm/h (S D 7.9) i.e. levels similar to or lower than those in the total population sample.

Table V Number of participants and non participants in 1974-75 among women with ESR  $\geq 30$  mm/h in 1969-69 who had or had not an explanation for the raised ESR at that time

	Possible explanation in 1968-69	No probable explanation in 1968-69
Non participants in 1974-75	9	4
Dead	3	1
Other	6	3
Participants in 1974-75	27	38
ESR $\geq 30$ mm/h in 1974-75	20	15
ESR $< 30$ mm/h in 1974-75	7	23

Table VII shows ESR in 1968-69 and the diagnoses of 11 women who at that time were not known to have cancer but who died from cancer between the two studies. Their average ESR (mean 9.0 mm/h, S.D. 4.3) was not higher than that of other women in the population sample.

## DISCUSSION

### ESR in previous population studies

There are few previous data on ESR in subjects who are representative of the general population in the area studied. In one previous Swedish study from Kristianstad (13) the ESR of women was reported to be similar to that found in our study but another Swedish population study from Eskilstuna (16) using the Wintrobe method reported somewhat higher values. In both the above studies ESR was found to increase with age and to be higher in women than in men. We also found a somewhat higher mean ESR in 50-year-old women (12 mm/h) compared with that 8 mm/h reported from Göteborg in men of the same age who had been studied by the same techniques (19).

### Definitions of normal and high ESR

Westergren (21) was the first to discuss an upper normal limit for ESR—7 mm/h in women—but later he proposed that 10-12 mm/h and even higher for patients above 50 years of age might be a more practical limit in clinical use. Borchgrewink et al (3) studied ESR in a Norwegian series of blood donors 1390 of whom were women. In agreement with

Table VI ESR in 1968-69 of women in a study in 1968-69 or in the interval up to the examination in 1974-75 were found to have cancer or gynaecological cancer (same time of the study in 1974-75)

M.d. = missing data

Subj no	Year of diagnosis	Age at the time of diagnosis (y)	ESR (mm/h) 1968-69
<i>Breast cancer</i>			
1	1968	60	5
2	1969	47	8
3	1970	52	5
4	1970	56	18
5	1971	49	3
6	1973	51	22
7	1973	65	13
8	1974	60	17
9	1974	60	9
10	1974	60	3
<i>Gynaecological cancer</i>			
1	1968	46	7
2	1970	40	28
3	1970	48	17
4	1971	53	2
5	1972	42	2
6	1973	43	14
7	1973	51	17
8	1974	52	4
9	1974	52	11

previous studies they found that ESR increased with age and they proposed 20 mm/h as a screening limit for female blood donors. In the Swedish study (6) of 1011 female

Table VII ESR in 1968-69 of women with diagnosis of cancer at that time but who had no cancer before the second examination in 1974-75

Subj no	Year of death	Age at death (y)	Diagnosis
1	1970	48	Bronchial cancer
2	1970	56	Glioblastoma
3	1971	53	Uterus cancer
4	1972	53	Ovarian cancer
5	1972	57	Vesical cancer
6	1973	42	Breast cancer
7	1974	43	Breast cancer
8	1973	50	Ovarian cancer
9	1974	55	Uterus cancer
10	1974	56	Ovarian cancer
11	1974	66	Intestinal cancer

employees ESR was also found to increase with age and the values were somewhat higher than in the present study. The authors suggest that the upper normal limit in women should be 20 mm/h below the age of 50 and 30 mm/h above 50.

An expert Panel on the ESR set up by the International Committee for Standardization in Hematology (10) has not fixed limits for normal ESR. It stated that a range which includes 90 or 100 mm/h for the local healthy population should be considered normal and that this limit should be fixed nationally or regionally. Their proposal is well in line with our arbitrary definition of high ESR as  $\geq 30$  mm/h which was found in 78 (5.3%) of 1461 women in 1968-69 and in 141 (10.9%) of 1295 in 1974-75. The arbitrarily chosen cutting level agreed well with the borderline levels for the centiles of ESR in women below the age of 50 and for the upper 10 centiles in women above 50.

#### Relation to age

In previous workers (3, 6, 13, 16) we found in cross-sectional as well as longitudinal studies that ESR increases with age. This means that the changes with age are mainly real and not cohort effects. Our results also showed that the changes in ESR values were mainly caused by small changes in individual participants and not by large changes in the population. The intra-individual differences were evenly distributed on both sides of the mean differences and the vast majority of values were near the mean.

#### Relation to other laboratory data

The association between raised ESR and decreased hemoglobin and Hct is well documented (6, 15, 22) and confirmed by our results. We also found statistically significant differences in serum iron levels and transferrin saturation between women with and without raised ESR (low values with raised ESR). Leucocyte counts were higher in women with raised ESR but differences were statistically significant only in the upper age groups in the total population. This means that if high ESR and leucocyte counts are considered to reflect acute inflammation, such infections are not main reasons for raised ESR.

We found no or only a slight association between raised ESR and high cholesterol and triglyceride levels. Bottiger (4) found a significant relationship

between ESR and serum lipids and Bottiger et al. (5) that ESR was significantly raised in apparently healthy persons who at the time of a health examination were markedly hyperlipidaemic. An association between increased lipid levels and raised ESR has also been reported by some investigators (15, 18) but not by some others (14). This discrepancy between studies might be explained by different ways of analyzing the data. We did not find any significant differences in lipid levels between women with and without increased ESR except for triglycerides in the case of women aged 54 and in the total sample. We plan to study this question in more detail in a subsequent paper.

#### Clinical significance of increased ESR

During the last 50 years it has been generally accepted that a healthy person should have a normal ESR and the ESR examination has been used all over the world to separate disease from health. The possibility has been discussed that a raised ESR might be caused by a hidden disease (4) or by a bad state of nutrition (15). In the study by Pincherle and Shanks (15) all but three of 41 subjects with an ESR  $>20$  mm/h had an apparent cause for the raised level. Borchert et al. (3) found among blood donors 47 women with ESR  $>20$  mm/h, 20 of whom had no probable explanation for the increase. This finding is in agreement with the present study where more than half of the women with ESR  $\geq 30$  mm/h had no apparent cause in either 1968-69 or 1974-75.

Increased ESR did not lead to a new diagnosis in any of the 1461 women studied in 1968-69 even though they were examined in many other respects too. The follow up study six years later showed that no diagnosis had been missed which could have explained the raised ESR in 1968-69. New diagnoses were recorded at the follow up in seven women with ESR  $\geq 30$  mm/h in 1968-69 who at that time had no probable explanation for an increased ESR but it is to be noted that six of them had an ESR  $<30$  mm/h at the follow up. Furthermore, women in whom cancer was detected later had no higher ESR in 1968-69 than the other participants in the population study.

The outcome for the women in the present study agrees with that for a male population in Goteborg (19) for which a long term follow up did not reveal any difference in ESR between those who died later and those who remained healthy. In contrast to the

view of Pincherle and Shanks (15) we conclude that the ESR is of limited value as a screening method in health surveys and may be omitted in such studies

### ACKNOWLEDGEMENT

The study was supported by grant no. 27X-4578 from the Swedish Medical Research Council

### REFERENCES

- 1 Bengtsson C, Blohmé G, Hallberg L, Hallström T, Isaksson B, Korsan Bengtson K, Rybo G, Tibblin E, Tibblin G & Westerberg H. The study of women in Gothenburg 1968-1969—a population study. *Acta Med Scand* 193: 311, 1973
- 2 Bengtsson C, Hallberg L, Hallström T, Hultborn A, Isaksson B, Lennartsson J, Lindquist O, Lindstedt S, Noppa H, Redvall L & Samuelsson S. The population study of women in Göteborg 1974-1975—the second phase of a longitudinal study. *Scand J Soc Med* 6: 49, 1978
- 3 Borchgrevink Ch F, Heistå H & Reimers Reksten K. Jr Senkningsreaksjonen som screening test for blodgivere. *Nord Med* 74: 1079, 1965
- 4 Böttiger L E. Erythrocyte sedimentation rate and plasma lipids. *Acta Med Scand* 193: 53, 1973
- 5 Böttiger L E, Carlsson L A, Ekelund L G & Olsson A G. Raised erythrocyte sedimentation rate in asymptomatic hyperlipidaemia. *Br Med J* 2: 681, 1973
- 6 Böttiger L E & Svedberg C A. Normal erythrocyte sedimentation rate and age. *Br Med J* 2: 85, 1967
- 7 Fåhræus R. Über die Ursachen der verminderten Suspensionsstabilität der Blutkörperchen während der Schwangerschaft. *Biochem Z* 89: 355, 1919
- 8 Herbert V, Gottlieb W, Lan K S, Fisher M, Gevritz N R & Wasserman L R. Coated charcoal assay of unsaturated iron binding capacity. *Med* 67: 855, 1966
- 9 International Committee for Standardized Haematology. Proposed recommendations for measurement of serum iron in human blood. *Haematol* 20: 541, 1971
- 10 — Recommendation for measurement of sedimentation rate of human blood. *Acta Med* 68: 505, 1977
- 11 Levine J B & Zak B. Automated determination of serum total cholesterol. *Clin Chim Acta* 1
- 12 Lofland Jr H B. A semiautomated method for the determination of triglycerides in serum. *Biochem* 9: 393, 1964
- 13 Nilsson S E, Lindholm H, Bales J N, Emilsson T & Stenkula G. The survey. *Acta Med Scand (Suppl)* 423: 19
- 14 Ohlson B & Rundqvist O. Über die Plasmalipoide für die Suspensionsstabilität. *Biochem Z* 247: 249, 1932
- 15 Pincherle G & Shanks J. Value of sedimentation rate as a screening test. *Br Med* 21: 133, 1967
- 16 Rigner K, G. Brante, G. Olafsson O. A population study (Eskilstuna 1964) set to evaluate the possible gains of health. *Acta Med Scand (Suppl)* 1: 55, 1969
- 17 Scheffe M. The analysis of variance. York 1959
- 18 Theorell H. Studien über die Plasmalipoide. *Biochem Z* 223: 1, 1930
- 19 Tibblin G, Wilhelmsen L & Werk factors for myocardial infarction and ischaemic heart disease and other. *Cardiol* 35: 514, 1975
- 20 Westergren A. The technique of sedimentation reaction. *Am Rev Tuberc*
- 21 — The erythrocyte sedimentation rate: variations of the technique. *Triangle* 3: 10, 1
- 22 Wintrobe M M. Macroscopic examination of blood. *Am J Med Sci* 185: 58, 1913

# Small Cell Carcinoma of the Lung

## Relation of Calcitonin to Bone Marrow Metastases, Parathormone and Gastrin

Mogens Hansen Jens F Rehfeld and Flemming Stadil

From Department of Chemotherapy, RII-RV Finsen Institute, Departments of Internal Medicine C and Clinical Chemistry, Bispebjerg Hospital, and Department of Surgery, D Herlev Hospital, Copenhagen, Denmark

**CT** The relations of calcitonin concentration, the presence of bone marrow metastases and concentrations of calcium, parathormone and gastrin in serum were investigated in 74 untreated patients with small cell carcinoma of the lung. Calcitonin concentrations were enhanced in two thirds of the patients while serum calcium concentrations remained normal. In 19 of 57 patients parathormone concentrations were slightly above the normal range. Concentrations of parathormone and calcitonin were not correlated. Bone marrow metastases had no influence on the concentration of serum calcitonin. Finally, a small inverse correlation between concentrations of gastrin and calcitonin in serum was observed. The results resemble those of the calcitonin producing medullary carcinoma of the thyroid supporting the suggestion of an ectopic hypercalcitoninemia in small cell carcinoma of the lung.

**Key words:** bone metastases, calcitonin, gastrin, PTH, small cell carcinoma.

Acta Med Scand 206 215 1979

Hypercalcitoninemia has been found in malignant tumors, in particular in patients with medullary carcinoma of the thyroid (1-13) and lung (8, 10) and other cancers (5, 9). The hypercalcitoninemia in medullary cancer appears to be related to the histologic type of tumor. Thus Silva et al (10) found particularly high concentrations of serum calcitonin in patients with small cell carcinoma and adenocarcinoma of the lung and in a previous study two thirds of patients with small cell carcinoma had hypercalcitoninemia at the time of diagnosis (8). The relation between hypercalcitoninemia and cell type of cancer may be indirect, as the frequency of

bone metastases is higher in patients with small cell carcinoma and adenocarcinoma than in patients with carcinomas of other cell types (7).

Accordingly we found it worthwhile to study the relation of serum calcitonin to the occurrence of bone marrow metastases in patients with small cell carcinoma. In addition the concentrations of calcium, parathormone and gastrin in serum were measured since these substances influence calcitonin secretion.

### PATIENTS AND METHODS

Blood samples were taken after an overnight fast from 74 patients with untreated small cell carcinoma of the lung. The concentrations of calcitonin (1), parathormone (4), gastrin (12) and calcium in serum were determined. Parathormone was analysed in 57 and gastrin in 69 of the patients.

The patients underwent a clinical staging program to disclose the extension of the disease outside one lung and mediastinal and supraclavicular lymph nodes (advanced disease). In addition to clinical and biochemical routine investigations at least chest X-ray, one bone marrow biopsy with aspiration from the posterior iliac crest and pentoscoping with liver biopsy were performed. According to the results of these staging procedures patients were divided into 3 groups: (R) patients with regional disease, i.e. confined to one lung, mediastinal and supraclavicular lymph nodes; (A) patients with advanced disease but without verified bone marrow metastases; and (B) patients with histologically verified bone marrow metastases.

### RESULTS

All serum calcium concentrations were below the upper limit of the reference value (2.20-2.70 mmol/l). In 4 patients serum calcium was just below the lower limit, the lowest value being 2.13 mmol/l, but concomitant hypoalbuminemia was found in all



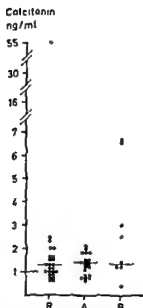


Fig 1 Concentrations of serum calcitonin related to stage of disease in patients with untreated small cell carcinoma of the lung. R=regional disease (confined to one lung and mediastinal and supraclavicular lymph nodes) A=advanced disease without verified bone marrow metastases B=advanced disease with histologically verified bone marrow metastases. The normal upper limit of serum calcitonin is 1 ng/ml (mean +2 S D)

these 4 patients. The median serum calcium value for all patients was 2.40 mmol/l.

Fig 1 shows calcitonin concentration in relation to stage of disease and bone marrow involvement. Considering the distribution of calcitonin concentrations and median values, no significant differences were observed between the three groups.

In Fig 2 the concentrations of parathormone are related to calcitonin concentrations. One third of the patients had slightly elevated levels of parathormone but no correlation between parathormone and calcitonin concentrations was found either in patients with or without verified bone marrow involvement.

Fig 3 shows the relation between gastrin and calcitonin concentrations in serum. Increased gastrin concentrations are related to the low levels of calcitonin while gastrin is within the normal range in most patients with significantly elevated serum calcitonin ( $p=0.10$  Spearman test).

## DISCUSSION

A relation between gastrin and calcitonin in serum has been noticed previously in patients with neo-

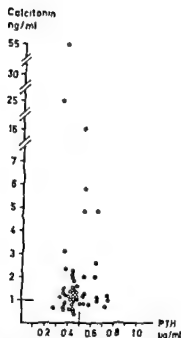


Fig 2 Basal concentrations of calcitonin and parathormone in serum from 57 patients. ●=patients with bone marrow metastases. The normal upper limit of parathormone is 0.5 pg/ml.

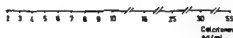
plastic diseases e.g. calcitonin concentrations in serum were significantly elevated in patients with gastrin-producing tumors while gastrin concentrations were significantly decreased in patients with calcitonin-producing medullary carcinoma of the thyroid (11). In the present investigation no correlation between gastrin and calcitonin concentrations appeared similar to that observed in medullary carcinoma of the thyroid.

Hypercalcemia is extremely rare in patients with small cell carcinoma of the lung (3) and 2 of the 5 patients in this study had normal concentrations of calcium. The concentration of calcitonin was decreased in two thirds of the patients and displayed concentrations otherwise seen in patients with medullary carcinoma of the thyroid (11). It is difficult to explain this observation by elevated parathormone because the basal concentrations of calcitonin and parathormone did not correlate. Deftos and Parthomore (6) did not find a correlation between basal concentrations of parathormone and calcitonin in patients with medullary carcinoma of the thyroid. In their study parathormone concentrations were elevated in patients with hyperplasia of the parathyroid glands and hypercalcemia while their remaining pa-

thyroid origin which is in contrast to the findings in patients with small cell carcinoma where hypercalcitoninemia appears to be related to an ectopic source of calcitonin (10). This was further evidenced by the demonstration of calcitonin in tumour tissue from two patients with small cell carcinoma (2) and is supported by the results presented here.

## ACKNOWLEDGEMENTS

The work was supported by King Christian X's Foundation and the Danish MRC.



basal concentrations of gastrin and calcitonin in 69 patients. The normal upper limit of gastrin is 10 pmol/ml (mean + 2 S.D.).

Calcitoninemia had normal calcium and gastrin concentrations. Thus the present findings resemble those from patients with calcitonin-producing medullary carcinoma of the thyroid. Although two thirds of our patients had hypercalcemia, only 19% had histologically verified bone metastases. Bone marrow biopsy with trephine as performed in this study is the most reliable to demonstrate bone marrow involvement in small cell carcinoma of the lung (7) and some of our patients with histologically verified bone marrow metastases did have normal calcitonin concentrations (Fig. 1). Consequently calcitonin concentrations were related neither to the presence of bone metastases nor to the extension of the disease.

Other authors (10) have also demonstrated hypercalcemia in patients with lung cancer. Except for cases of epidermoid carcinoma with marginally elevated concentrations, all their cases with elevated serum calcitonin were confined to patients with adenocarcinoma and small cell carcinoma. However, it appears from their data that patients with adenocarcinoma and hypercalcitoninemia usually had verified bone metastases. This difference between small cell carcinoma and adenocarcinoma appears to be fundamental. So hypercalcitoninemia in adenocarcinoma seems to be of

## REFERENCES

1. Almquist S, Telenius Berg M & Wasthed B. Serum calcitonin in medullary thyroid carcinoma. Radioimmunoassay technique and diagnostic value. *Acta Med Scand* 196; 177-194.
2. Baylin S B, Weisburger W R, Eggleston J C, Mendelsohn G, Beaven M A, Abeloff M D & Ettinger D S. Variable content of histaminase, L-dopa decarboxylase and calcitonin in small cell carcinoma of the lung. *N Engl J Med* 299: 105-1978.
3. Bender R A & Hansen H H. Hypercalcemia in bronchogenic carcinoma. A prospective study of 200 patients. *Ann Intern Med* 80: 205-1974.
4. Christiansen C, Bastrup P C, Lindgren P & Transbol I. Endocrine effects of lithium. Primary hyperparathyroidism. *Acta Endocrinol* 88: 528-1978.
5. Coombes R C, Easty G C, Deure S I, Hillyard C J, Stevens U, Girgis S I, Galante L S, Heywood L, MacIntyre I & Neville A M. Secretion of immunoreactive calcitonin by human breast carcinomas. *Br Med J* 4: 197-1973.
6. Deftos L J & Parthomore J G. Secretion of parathyroid hormone in patients with medullary thyroid carcinoma. *J Clin Invest* 54: 416-1974.
7. Hansen H H. Bone metastases in lung cancer. Munksgaard Copenhagen 1974.
8. Hansen M, Hansen H H & Tryding N. Small cell carcinoma of the lung. Serum calcitonin and serum histaminase (diamine oxidase) at basal levels and stimulated by pentagastrin. *Acta Med Scand* 204: 257-1978.
9. Silva O I & Becker K I. High plasma calcitonin levels in breast cancer. *Br Med J* 4: 60-1976.
10. Silva O I, Becker K I, Trimmack A, Doppman J L & Snider R H. Increased serum calcitonin levels in bronchogenic cancer. *Chest* 69: 495-1976.
11. Sizemore G W, Go V I W, Kaplan P L, Sanzenbacher I J, Holtenmüller K H & Arnaud C. Relations of calcitonin and gastrin in the Zollinger-Ellison syndrome and medullary carcinoma of the thyroid. *N Engl J Med* 288: 641-1973.
12. Stuhli P & Rehfeld J F. Determination of calcitonin in serum. *Scand J Gastroenterol* 8: 101.

- 13 Tashjian A H, Howland B G, Melvin K E W & Hill C S. Immunoassay of human calcitonin. Clinical measurement: relation to serum calcium and studies in patients with medullary carcinoma. *N Engl J Med* 283: 890, 1970.
- 14 Telenius-Berg M. Diagnostic studies in carcinoma of the thyroid. New methods of diagnosis in families with Sipple's syndrome. *Med Scand (Suppl)* 597, 1976.

# Multiple Attacks of Jaundice Associated with Repeated Sulfonamide Treatment

Sten Iwarson and Per Lundin

From the Department of Infectious Diseases Östra Sjukhuset and the First Department of Pathology Sahlgrenska Sjukhuset University of Göteborg Göteborg Sweden

**ACT** Four women who were treated with sulfonamides because of recurrent urinary tract infections experienced adverse liver reactions with jaundice during their third, fourth and fifth course of treatment respectively. In spite of this, sulfonamide treatment was reinstituted some years later. Adverse reactions with jaundice recurred on all occasions. The clinical picture of the liver reactions was distinguishable from that of viral hepatitis and a drug-like reaction was also seen histologically. Fibrosis appeared histologically after a third attack of jaundice associated with sulfonamides in one patient but otherwise no persisting abnormalities were noted.

*Key words:* sulfonamide jaundice, drug jaundice.  
*Acta Med Scand* 206 219-1979

Drug-induced liver injury is a rare but considerable adverse reaction to sulfonamide treatment. A review of this problem published in 1967 (2) revealed 106 cases of sulfonamide-induced liver reactions, 96 of which occurred before 1947. This cannot be the true incidence since only 51 cases of sulfonamide-induced hepatic injury were notified in Sweden during 1954 (3). Recurrent jaundice after repeated exposure to sulfonamides has been reported in association with antibiotic provocative exposure. The present report describes four women in whom sulfonamide treatment was reinstituted in spite of previous experience of adverse liver reactions.

## PATIENTS AND METHODS

Four women, 20, 30, 35 and 68 years of age, had been previously treated with sulfonamides as well as other antibiotics because of recurrent urinary tract infections. In all four patients previous experience of adverse liver reactions in association with sulfonamide treatment with this drug was noted: in three cases once and in one case twice.

New attacks of jaundice occurred on all five occasions. The preparation concerned was on all occasions Sulfapral®—a combination of sulfamethizole and sulfamethoxypyridazine which has been widely used in Scandinavia during several years for treatment of urinary tract infections—in a standard dose of 2 tablets twice daily. The period of treatment before onset of jaundice was 2-9 weeks at their first attack of jaundice and 1-2 weeks at their second attack (Table I). The patients had received 2-4 courses of sulfonamide treatment previous to that during which jaundice first appeared.

Liver function tests were performed by standard techniques as described elsewhere (6). Liver biopsies were obtained by a modified Menghini technique. The histological alterations were classified according to suggestions by an international group (1). Presence of hepatitis B surface antigen in serum was analysed with a radioimmunoassay (Ausria II, Abbot Laboratories) and anti-HBs was determined by Ausab (Abbot Laboratories).

## RESULTS

The first attack of jaundice appeared during the third, fourth and fifth period of sulfonamide treatment respectively (Table I). The period of treatment before onset of jaundice was shorter during the second (mean 1.5 weeks) and third (mean 1 week) attacks than during the first (mean 5 weeks).

The initial symptoms during each attack were fatigue, nausea, vomiting and fever followed by dark urine and jaundice. The maximal levels of serum bilirubin, alkaline phosphatases and SGPT are shown in Table I. As a rule, high serum levels were rapidly reached after re-exposure to the drug. The duration of abnormal aminotransferase levels was 4-12 weeks (mean 7.7). Alkaline phosphatase levels were moderately raised on all occasions but had no correlation to histological alterations of bile stasis. In all four patients the galactose tolerance test showed a normal half life of galactose (9-14 min) at about the time when the aminotransferase levels had returned to normal.

Table 1 Maximal levels of serum bilirubin, alkaline phosphatases and SGPT, duration of attack, levels in serum and histological abnormalities in liver biopsies

Case no	Period of sulfonamide treatment	Duration of treatment before appearance of jaundice (weeks)	Maximal level of			Duration of abnormal SGPT levels (weeks)	Liver histology
			Serum bilirubin (mg/ml)	Alkaline phosphatases (Buch units)	SGPT (IU)		
1	4	6	31.8	11	1 180	12	Hepatitis-like reaction with bile stasis, three attacks, fibrosis at the 2nd attack
	5	2	15.9	10	1 830	10	
	6	1	25.1	13	1 810	9	
2	5	3	7.4	14	600	8	Hepatitis-like reaction and in addition eosinophilia at 7 days
	6	2	9.2	12	1 540	4	
3	4	9	10.7	10	1 800	8	Hepatitis-like reaction and in addition stasis at 1st attack
	5	1	3.5	13	576	5	
4	3	2	6.7	16	870	7	Hepatitis-like reaction, biopsy not performed during 2nd attack
	4	1	3.0	15	570	6	
Normal value			$\leq 1.0$	$< 8$	$< 25$		

A hepatitis-like reaction with moderate or prominent parenchymal cell damage (single cell necrosis, hydropic degeneration and ballooning) was seen in all liver biopsies. Portal inflammatory infiltration with mononuclear cells, and in one case eosinophilia, was also observed. A more or less apparent Kupffer cell reaction was present in all biopsies and in some cases signs of bile stasis as well (Table I and Figs 1-3). The histological alterations during the second attack were as a rule not more prominent than during the first. However, discrete signs

of chronicity with slight fibrosis were known cases during the second attack. The patient had a third exposure and a third attack, which showed a more prominent fibrosis in the liver biopsy. However, the liver architecture was altered.

## DISCUSSION

It has long been known that drug hypersensitivity reactions may also manifest

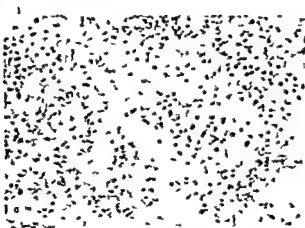


Fig. 1 Case 3. First attack. (a) Hepatitis-like picture with disarray of the architecture, inflammatory cell infiltration and Kupffer cell proliferation ( $\times 120$ ). (b) Parenchymal cell

damage with hydropic degeneration and basophilic multinuclear hepatocytes are visible ( $\times 220$ ).



ase 3 Second attack (a) In principle the same as at the first attack ( $\times 170$ ) (b) Pronounced lular damage with single cell necrosis ( $\times 270$ )



actions (7) This type of liver damage has suggested to occur with a frequency of 0.01. The true incidence is not known because nosology is difficult to verify. It has so far been able in most cases to distinguish this type of action from viral hepatitis. Now when chemical methods for differentiating hepatitis A and B from other types of hepatitis are available, this difficulty is at least partly overcome. In primary attacks of jaundice in our four patients all diagnosed as viral hepatitis. When a relapse of jaundice occurred after administration of the same sulfonamide preparation, it was understood that also the first attack was probably associated with sulfonamide treatment.

The patients were all HBsAg negative during their attacks of jaundice and did not develop anti-HBs during convalescence. No test for hepatitis A virus was available at the time when these cases were diagnosed (in 1971-75). However, there was no hepatitis contact, foreign travel or other factor speaking in favour of hepatitis A infection.

Different histological abnormalities have been reported in association with sulfonamide-induced liver reactions. In most cases areas of hepatocellular necrosis with inflammatory infiltration and sometimes eosinophilia have been reported (7). The hepatocellular injury is in many cases accompanied by cholestatic features. Also a more chronic type of liver damage has been described (8).



ase 4 Second attack (a, b) Fairly pronounced reaction with a tendency to septal proliferation ( $\times 100$ ) (Fig. b  $\times 220$ )



The liver biopsies of all our four patients have shown signs of hepatocellular damage with mononuclear inflammatory reaction and cholestasis has been seen in six biopsies. We have called this a hepatitis like reaction. Signs of a more chronic process have been slight with some fibrosis but no picture of chronic aggressive hepatitis.

Repeated exposure to a drug entails a greater risk of sensitization and this is a major problem in patients with recurrent urinary tract infections. They are as a rule exposed to several drugs on repeated occasions. Once sensitized the patient may react vigorously also after a small challenging dose. Thus the benefits of establishing a correct diagnosis must be weighed against the potential harm of a provocative exposure.

Besides the allergic type of liver reaction a direct toxic effect of sulfonamides has been assumed to contribute to the liver damage. However the present cases as well as others reported in the literature seem to favour the hypothesis of a mechanism of acquired hypersensitivity (2, 3). The occurrence of a latent period between the beginning of administration of the drug and the development of the clinical manifestations of hepatic injury strongly favour the hypersensitivity theory. Further this type of liver damage does not seem to be dose-dependent which might be expected for a pure toxic liver reaction.

Pre-existing liver damage is not considered a con-

traindication to the use of sulfonamides. A liver reaction has once occurred a further treatment (and challenge) should be avoided. Awareness of potential sensitization and recognition of its clinical manifestations is of continuing importance.

## REFERENCES

- 1 Branch L, De Groote J, Desmet V J G, Korb G, Popper H, Paulsen H & Schmidt M. Thaler H & Wepler W. Criteria in viral hepatitis reviewed by an international group. *Lancet* i 333 1971.
- 2 Dujovne C A, Chan C H & Zieve A. Sulfonamide hepatocellular injury. *N Engl J Med* 1967.
- 3 French A J. Hypersensitivity in the pathogenesis of the histopathologic changes associated with sulfonamide chemotherapy. *Am J Pathol* 1972.
- 4 Furhoff A K (ed). *Hepatitis etiology*. Medd nr 75 fr Lakemedelbetraktning 1976.
- 5 Goodman L S & Gilman A (eds). *Pharmacological basis of the therapeutic use of drugs*. New York 1975.
- 6 Iwarson S. Studies on viral hepatitis (Australoantigen). *Scand J Infect Dis Suppl* 1974.
- 7 Tisdale W A. Focal hepatitis fever following therapy with sulfamethoxazole long acting sulfonamide. *N Engl J Med* 1974.
- 8 Tonder M, Nordøy A & Elgjo K. Sulfonamide induced chronic liver disease. *Scand J Clin Lab Invest* 1974.

# Streptozotocin Treatment of a Pancreatic Tumour Producing VIP and Gastrin Associated with Verner-Morrison Syndrome

K. Öberg H. Bostrom J. Fahrenkrug J. F. Dymling  
O. B. Shaffalitsky de Muckadell and G. Lundqvist

From the Departments of Internal Medicine and Clinical Chemistry, University Hospital, Uppsala; the Department of Endocrinology, Malmö General Hospital, Malmö, Sweden; and the Department of Clinical Chemistry, Bispebjerg Hospital, Copenhagen, Denmark.

**ACT** A 57-year-old male patient with a non-beta islet cell carcinoma of the pancreas is described. Both gastrin and VIP levels were elevated and the patient suffered from a watery diarrhoea of pancreatic cholera and hyperacidity. Stool contained gastrin and VIP as demonstrated by immunofluorescence. The patient also had a history of familial renal stone formation and parathyroid nodular hyperplasia. Resection of pancreatic tumour in 1973 resulted in four years without symptoms. In 1977 definite signs of multiple hepatic metastases appeared. These signs disappeared after streptozotocin given in a dosage of 2 g three times at 2-week intervals. The patient has remained well for 18 months after this treatment. The causative agents of the clinical syndrome in this case are discussed in relation to circulating hormone levels.

**Key words:** Verner-Morrison syndrome, VIP, gastrin, streptozotocin treatment.  
*Acta Med Scand* 206: 223-227, 1979.

The syndrome of watery diarrhoea, hypokalaemia, achlorhydria (WDHA syndrome, pancreatic cholera or Verner-Morrison syndrome) associated with a non-beta islet cell tumour of the pancreas was first described by Verner and Morrison in 1958 (24). In almost all of the cases are associated with islet cell tumours, the syndrome can be produced by various tumour types (20). The causative agent is still not firmly established, although the presence of increased plasma and tumour concentrations of vasoactive intestinal polypeptide (2, 20), a 28 amino acid peptide (21) known to produce the symptoms seen in this syndrome, favour the role of VIP. In some patients, however, the

hormonal overproduction involves more than one humoral agent. A few cases have been reported in which the responsible agent is supposed to be pancreatic polypeptide (PP) (13) or prostaglandin E<sub>2</sub> (9).

Streptozotocin, an antitumour antibiotic, has recently been used successfully in the treatment of the WDHA syndrome (6, 11, 22). In this report we describe successful streptozotocin treatment of a patient with a pancreatic carcinoma producing both VIP and gastrin.

## CASE REPORT

A male, born in 1920, was surgically explored in 1969 because of renal stones and severe hypercalcaemia (S-Ca >3.0 mmol/l). Two macroscopically normal parathyroids were left intact and one macroscopically enlarged parathyroid was removed. Morphologically this demonstrated a nodular hyperplasia consisting partly of oxyphilic cells and partly of chief cells. S-Ca returned to normal after operation. His father and two brothers, one of whom had been operated on for parathyroid hyperplasia, had had recurrent renal stones.

In Nov. 1972 the patient complained of recurrent short episodes of watery diarrhoea since July. The S-Ca was normal at this time. In Dec. a gastric ulcer was diagnosed which healed on conservative medical treatment. S-Ca was still normal. In June 1973 he became acutely ill and was readmitted to Malmö General Hospital with abdominal pains and large watery diarrhoeas 9-10 times daily. Laboratory tests revealed severe dehydration, hypercalcaemia and hypokalaemia. His general condition

**Abbreviations:** WDHA syndrome = the syndrome of watery diarrhoea, hypokalaemia and achlorhydria; VIP = vasoactive intestinal polypeptide; PP = pancreatic polypeptide; ZE syndrome = Zollinger-Ellison syndrome.



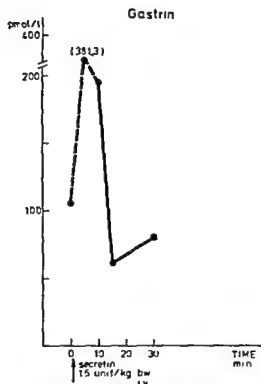


Fig 1 Serum gastrin after administration of secretin as a bolus injection

deteriorated in spite of i.v. fluid supplements. The stool volume varied between 5 and 8 l per day. In the Intensive Care Unit the patient required respiratory assistance and approximately 10 l of fluid intravenously including 200–400 mmol of potassium daily. The fasting secretion of hydrochloric acid was very high and a large duodenal ulcer was found.

Angiography of the coeliac artery yielded a large, partly calcified tumour in the pancreatic tail. On laparotomy in July 1973 a partial resection of the pancreas was performed. There were no macroscopical metastases in the liver or the other abdominal organs. Morphologically the resected part of the pancreas contained three separate non-beta islet cell carcinomas. Immunofluorescent studies demonstrated a positive reaction with antibodies to VIP and gastrin. Postoperatively the patient recovered completely clinically.

The patient remained well but slightly hypercalcaemic until March 1977. At that time the diarrhoeas recurred rather abruptly. He was admitted in early April with four or five diarrhoeas daily and had at that time experienced a weight loss of 6 kg. He deteriorated rapidly after admission. Multiple liver metastases were visualized on scintigraphy and angiography.

He was referred to the Medical Department, University Hospital Uppsala, in May 1977. At that time stool volumes varied between 2 and 9 l daily. The basal gastric acid output was low (0  $\mu\text{mol}/\text{min}$ ) and after pentagastrin stimulation 136  $\mu\text{mol}/\text{min}$  (normal response). X-rays of the sella turcica and lungs as well as computer tomography of the skull were normal.

The patient was initially treated with electrolytes (potassium 80–170 mEq/d) and fluids (4–6 l/d). Thereafter a course of streptozotocin was given intravenously in three doses of 1 g each over one week. Already after two doses he formed stool daily.

Three months later he had gained 7 kg and laboratory test values had become normal except for PP and S-calcium.

At reexamination 20 months after surgery the patient was quite well and had resumed ordinary work. Computer tomography of the chest and liver scintigraphy as well as laboratory tests except for S-Ca which remained slightly elevated and S-PTH which was elevated to 0.54  $\mu\text{g/l}$ .

The patient fulfils the criteria of endocrine adenomatosis type I with pancreatic islet cell hyperplasia of parathyroids.

## LABORATORY METHODS

Routine haematological and serum analyses were performed at the Laboratory of Clinical Chemistry, University Hospital Uppsala. Gastrin, PP, VIP and S-Ca were determined by radioimmunoassay (range 7–16).

## LABORATORY RESULTS

The laboratory findings before and after treatment are summarized in Table 1. Gastrin, PP and VIP levels were found normal.

Because of hypergastrinaemia, existence of ventricular and duodenal ulcers and hyperacidity a secretin test was performed, shown in Fig. 1. Secretin injection caused

Table 1 Laboratory tests before and after treatment with streptozotocin

	Before	After
ESR (mm/h)	47	15
b-Hb (g/l)	96	125
S-albumin (g/l)	30	42
S-calcium (mmol/l)	2.74	2.85
S-phosphate (mmol/l)	0.8	1.1
S-potassium (mmol/l)	2.7	3.8
S-sodium (mmol/l)	140	142
Sb-glucose (mmol/l)	5.0	4.1
S-gastrin (pmol/l)	114.7	1.5
S-PP (pg/ml)	666	1.5
p-VIP (pmol/l)	210	0.5
p-somatostatin (pg/l)	78	0.5
S-PTH ( $\mu\text{g/l}$ )	0.35	0.5
S-calcitonin (pmol/l)	480	100

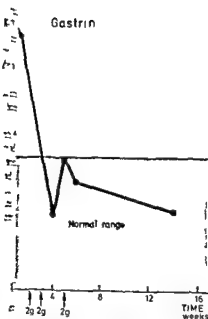


Fig 2 Serum gastrin levels on different occasions during streptozotocin treatment

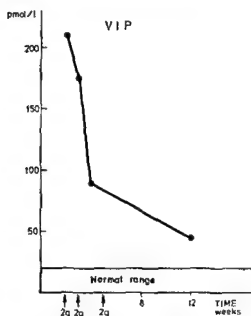


Fig 3 Plasma VIP levels on different occasions during streptozotocin treatment and three months after

1 increase in serum gastrin concentration a  
2 comparable to that seen in patients with  
3 r Ellison (ZE) syndrome  
4 the streptozotocin treatment gastrin and  
5 els decreased successively leading to a  
6 ation of serum gastrin concentration after  
7 two doses while the VIP level was still  
8 ely increased after the final treatment (Figs  
9 ) PP levels however increased during  
10 it (Fig 4)

## DISCUSSION

1 endocrine tumours of the pancreas have the  
2 ty of multiple hormone production as shown  
3 by immunocytochemical investigations (12 18)  
4 h this multihormonal production might re  
5 difficulties it has also been stated  
6 clinical symptoms are often caused by  
7 duction of one hormone only (13)  
8 present case the history of peptic ulcers  
9 viously demonstrated gastric hyperacidity  
10 r with hypergastrinaemia and a positive  
11 test suggest the presence of a gastrinoma  
12 (drome) while the increased VIP levels and  
13 symptoms of watery diarrhoea and electro-  
14 balance favour the diagnosis of a VIPoma  
15 Morrison or WDHA syndrome) Only one

case of bihormonal production of gastrin and VIP  
has to our knowledge been reported (10)

Streptozotocin treatment resulted in an im-  
mediate improvement of stool frequency accom-  
panied by a normalization of circulating gastrin  
levels and a decline of VIP levels. It could not  
however be stated whether the overproduction of  
gastrin and/or VIP caused the clinical symptoms of  
pancreatic cholera. The differential diagnosis be-  
tween the ZE syndrome and the Verner Morrison  
syndrome is often difficult since one third of the ZE  
patients have diarrhoea (4).

Earlier reports have demonstrated a beneficial  
effect of streptozotocin upon both VIP and  
gastrin producing tumours (6 22 23) in ac-  
cordance with the present finding. The increase in  
serum PP levels during streptozotocin treatment  
could possibly indicate an insensitivity of PP cells  
to streptozotocin. This assumption agrees with find-  
ings in a previous report where no effect was seen  
after treatment of a patient with a PP producing  
tumour (15).

Our patient initially demonstrated elevated  
levels of serum calcitonin 480 pmol/l. Following  
pentagastrin stimulation there was no further in-  
crease in the calcitonin levels. After treatment with  
streptozotocin serum calcitonin returned to values  
within normal limits. Hypercalcitoninaemia has

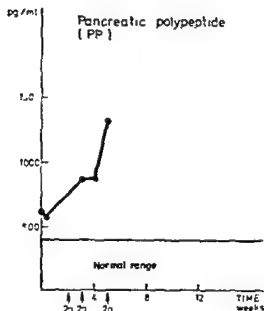


Fig. 4 Serum levels of PP on different occasions during streptozotocin treatment

previously been reported in VIPomas (19) and in a variety of tumours including pancreatic non islet cell carcinoma (3). Hypercalcaemia has also been observed in connection with VIPomas and seems to occur in nearly half the patients with pancreatic cholera (17).

The mechanism causing hypercalcaemia in our patient remains obscure. Medullary carcinoma of the thyroid can be ruled out since there were no indications of this disease during the prolonged observation period. Furthermore, pentagastrin stimulation is known to cause increases in serum calcitonin in this condition (8). Hypercalcaemia per se was considered very unlikely since hypercalcaemia persisted whereas serum calcitonin became normal. Glucagon, a peptide structurally and pharmacologically related to VIP, has been shown to release calcitonin in several animal species. However, his plasma glucagon levels were not elevated. PP may also be ruled out since the levels of PP increased following treatment, whereas calcitonin levels decreased. Gastrin has also been connected with calcitonin release and this remains a distinct possibility. If so, the patient might be assumed to have had a long standing hypercalcaemia causing hyperparathyroidism primarily of the secondary type followed by autonomous nodular hyperplasia (14). In case of hypercalcaemia secondary to elevated circulating

gastrin, a pentagastrin stimulation is expected to cause a further increase in calcitonin. However, the hypercalcaemia also be directly derived from the tumour.

The present case illustrates the need for a hormone assay for the diagnosis and treatment of patients with chronic diarrhoea due to tumours. Although streptozotocin treatment of malignant non beta islet cell tumours of the pancreas has to be studied further, it may have a beneficial value in cases where other alternatives are rather limited.

#### ACKNOWLEDGEMENTS

Supported by grants from the Swedish Medical Council (project no. 4534) and Astrid Karlsson.

#### REFERENCES

1. Arimura A, Lundqvist G, Rothman J E, Fernandez Durango R, Ekström R, G. Meyers C & Schally A V. Radioimmunoassay of somatostatin. *Metabolism (Suppl)* 11: 1974.
2. Bloom S, Polak J & Pearce A G. E. Intestinal polypeptide and water electrolyte syndrome. *Lancet* 2: 14, 1973.
3. Coombes R C, Hillyard C J, Green M, MacIntyre J. Plasma immunoreactive calcitonin in patients with non thyroid tumours. *Lancet* 1974.
4. Ellison E H & Wilson S D. The Zollinger-Ellison syndrome: Reappraisal and evaluation of registered cases. *Ann Surg* 160: 11, 1964.
5. Fahrenkrug J & Schaffalitzky de Mucke B. Radioimmunoassay of vasoactive intestinal peptide (VIP) in plasma. *J Lab Cl Med* 1977.
6. Gagel R, Costanza M, DeLella P, Bloom S, Miller H, Ucci A & Neri R. Streptozotocin treated VIPoma. Plasma vasoactive intestinal peptide and clinical response. *Arch Intern Med* 136: 149, 1976.
7. Hallgren R, Lundqvist G & Öberg K. Levels of human pancreatic polypeptide in pancreatic disease. *Scand J Gastroenterol* 12: 923, 1977.
8. Henessy J F. A comparison of pentagastrin infusion as provocative agent in the diagnosis of medullary carcinoma of the thyroid. *Endocrinol Metab* 19: 487, 1974.
9. Jaffe B M, Koppen D F, DeSjager K, Gingerich R & Gredler M. Intensive treatment of pancreatic cholera. *N Engl J Med* 1977.
10. Judge D, Demers L, Nathaniel D, Petrovski R & Trautwein S. Vasoactive intestinal peptide and gastrin-producing tumours. *Arch Pathol Lab Med* 101: 10, 1977.

- n R Levy A Gardner J Miller J Gordon Schein P Pancreatic cholera Beneficial effects of treatment with streptozotocin *N Engl J Med* 294:1 1975
- son L I Grmelius L Håkansson R Reh J F Stadil F Holst J Angervall L & Hller F Mixed endocrine pancreatic tumours producing several peptide hormones *Am J Pathol* 71 1975
- son L J Schwartz T Lundqvist G Chance E Sundler F Rehfeld J F Grmelius L Fahrenkrug J Schaffalitzky de Muckadell O & Hller N Occurrence of human pancreatic polypeptide in pancreatic endocrine tumours possible implication in the watery diarrhea syndrome *Am J Pathol* 85 675 1976
- berg O & Dymling J F Pathogenesis of Cushing's disease in thyroid gland *Acta Pathol Microbiol Scand (A)* 80:577 1972
- qvist G Krause U Larsson L I Grmelius L Schaffalitzky de Muckadell O Fahrenkrug J Hller N & Chance R E A pancreatic polypeptide producing tumour associated with the watery diarrhea syndrome *Scand J Gastroenterol* 13 715 1978
- qvist G & Wide L Serum gastrin determined with a radioimmunosorbent technique *Clin Chim Acta* 79 357 1977
- 17 Pessayre D Thesis University of Paris VII 1973
- 18 Polak J M Bloom S R Adrian T E Heitz P Bryant M G & Pearce A G Pancreatic polypeptide in insulinomas gastrinomas VIPomas and glucagonomas *Lancet* i 328 1976
- 19 Rambaud J Nisard A Modighani R Carmette C Moukhtar M S Hill P A & Bestman H Hypercalcaemia in VIP-omas *Lancet* i 20 1978
- 20 Said S I & Faloona G Elevated plasma and tissue levels of vasoactive intestinal polypeptide in watery diarrhea syndrome due to pancreatic bronchogenic and other tumours *N Engl J Med* 293 155 1975
- 21 Said S I & Mutt V Polypeptide with broad biological activity Isolation from the small intestine *Science* 169 1217 1970
- 22 Siegel S R & Muggia R M Treatment of pancreatic cholera *N Engl J Med* 293 198 1975
- 23 Stadil F Stage G Rehfeld J F Efsen F & Fischerman K Treatment of Zollinger Ellison syndrome with streptozotocin *N Engl J Med* 294 1440 1976
- 24 Verner J V & Morrison A B Islet cell tumour and a syndrome of watery diarrhea and hypokalaemia *Am J Med* 25 374 1958

2

# Changes in Serum Triglyceride and Cholesterol Levels during Long-Term Phenytoin Treatment for Epilepsy

P. V. Luoma, M. I. Reunanen and E. A. Sotaniemi

from the Clinical Research Unit, Department of Internal Medicine and the Department of Neurology, University of Oulu, Oulu, Finland

**ABSTRACT** The effect of long-term phenytoin on serum triglyceride and cholesterol levels in patients with epilepsy was investigated. In patients followed up for six years, phenytoin treatment was associated with an increase in serum triglyceride and cholesterol levels. The most significant increases in lipid levels were measured during the first months of therapy, whereafter values generally tended to stabilize.

The elevation in serum triglyceride concentration was relatively greater than that in serum cholesterol level. Cholesterol concentrations, however, remained high for a longer period. The results indicate that phenytoin therapy for epilepsy is associated with a rise in serum triglyceride and cholesterol levels, the degree of which seems to be related to the duration of the treatment. The changes probably reflect phenytoin effects on hepatic lipid metabolism.

**Key words:** triglycerides, cholesterol, phenytoin, epilepsy.

Acta Med Scand 206 229-1979

Like other drugs such as phenytoin or phenobarbital may alter liver function with an increase in the activity of the hepatic microsomal enzymes.

Phenytoin, which is involved in the metabolism of vitamins, hormones and lipids (2, 4, 6, 10), and studies with these compounds have demonstrated increases in serum lipid levels in healthy subjects and patients with epilepsy (4, 11). High serum triglyceride and cholesterol levels are considered as risk factors for cardiovascular diseases. Therefore, the follow-up of serum lipid levels in patients undergoing anticonvulsant treatment was considered important.

The present study was undertaken to evaluate the effect of phenytoin by comparing serum lipid levels before and after long-term phenytoin treatment. Serum triglyceride and cholesterol levels in a group of epileptics, some of whom have been followed up for six years, are reported.

## PATIENTS

Twenty consecutive patients, 9 men and 11 women, undergoing phenytoin treatment for epilepsy were investigated. The mean age of the males was 30.1 years (range 19-59) and of the females 35.5 years (range 17-64). Their serum triglyceride and cholesterol levels were determined before the commencement of phenytoin treatment and after one, three and six months of therapy, and then regularly at six-month intervals.

The patients live in the same area where dietary habits vary little. The diagnosis of epilepsy was based on case history and neurological findings. The daily phenytoin dose was 200-350 mg. The patients had no other regular drug treatment.

## METHODS

Blood samples for determination of serum triglyceride and cholesterol were drawn after an overnight fast. Serum lipid concentration was determined by standard auto-analyzer techniques (Technicon). The triglyceride assay used the method of Wahlefeld (14) and serum cholesterol assay the method of Huang et al. (7).

Student's *t* test for paired data was employed to calculate the significance of the results. In each patient, lipid values during therapy were compared with their own values before treatment.

## RESULTS

Phenytoin therapy was associated with a significant gradual increase in serum triglyceride level (Table I, Fig. 1). During the first month of therapy triglycerides increased by 25%. The highest mean concentration measured three months after commencement of the therapy. At that time triglycerides were 45% above the pretreatment level. Later the values decreased and did not differ significantly from the mean pretreatment values. Before treatment, four (20%) of the 20 patients had triglyceride concentrations of over 1.6 mmol/l. After one and three months of therapy, eight (40%) and seven (35%) patients, respectively, had high serum triglyceride levels.

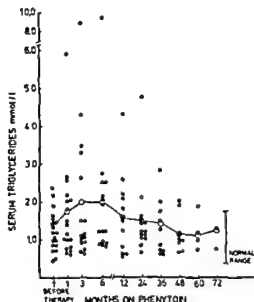


Fig. 1 Individual (●) and mean (○) serum triglyceride values before and during phenytoin treatment

There was a significant increase also in serum cholesterol concentration during phenytoin therapy (Table 1, Fig. 2). The increase during the first month was 14% and the values remained at this high level for two years. Serum cholesterol values exceeding 7.5 mmol/l were found in four patients before treatment and in nine and six patients after treatment for one and three months, respectively.

### DISCUSSION

Elevated serum cholesterol levels have been demonstrated in epileptics undergoing anticonvulsant therapy (1, 11). The present results show that therapy with phenytoin might be associated with temporary changes in serum triglyceride and

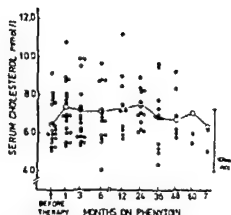


Fig. 2 Individual (●) and mean (○) serum cholesterol values before and during phenytoin treatment

cholesterol levels. In epileptics followed 6 years, there was an increase in serum triglyceride and cholesterol levels during the first 6 months of therapy, after which the values in most patients tended to decrease. The rise in serum triglyceride concentration was relatively greater than the increase in serum cholesterol level. Cholesterol, however, remained elevated for a longer time. Lipid values measured later did not differ from treatment levels. This suggests that the increase in serum lipid levels in phenytoin-treated subjects can be considered an adaptation phenomenon to the use of the drug.

The mechanism by which serum lipids increase in phenytoin-treated subjects is not known. The changes observed, however, may be secondary to drug effects on liver function and the metabolism of endogenous substances affecting lipids. The liver has a central role in the metabolism of serum lipids. Therapy with compounds

Table 1 Serum triglyceride and cholesterol levels (mmol/l) before and during phenytoin (PH) therapy for epilepsy

	Before PH	Duration of PH treatment (mo )							
		1	3	6	12	24	36	48	n
Triglycerides									
Mean	1.39	1.76**	1.99	1.96	1.95	1.49	1.39	1.11	18
S D	0.96	1.24	1.97	2.06	1.01	1.07	0.96	0.51	18
Cholesterol									
Mean	6.41	7.30 **	7.14***	7.12	7.23**	7.64*	6.67	6.49	18
S D	1.17	1.45	1.83	1.69	1.54	1.47	1.71	1.40	18
n	20	20	20	17	14	14	12	9	1

\* $p < 0.05$  \*\* $p < 0.01$  \*\*\* $p < 0.005$

phenytoin and phenobarbital may affect liver function. It causes proliferation of hepatic endoplasmic reticulum. This phenomenon may be associated with increased bile acid and hormone metabolism (10, 17, 13).

**Phenytoin treatment like phenobarbital therapy facilitates the absorption of lipid precursors, stimulating hepatic bile acid synthesis and bile acid excretion. The rate of triglyceride synthesis in the liver is regulated by the activity of the enzyme of the triacylglycerol pathway in which acyl-CoA oxidase is the rate limiting enzyme.**

(4) Phenytoin may stimulate phosphatidate hydroxylase and thus enhance triglyceride synthesis in hepatocytes. Stimulation of apolipoprotein synthesis in connection with enzyme induction could further facilitate the output of the liver and contribute to the elevation of lipid levels in serum.

In subjects with an increase in serum cholesterol in phenytoin therapy, subjects may reflect drug-induced increases in microsomal 3-hydroxy-3-methylglutaryl-CoA synthetase activity, which is the rate-limiting enzyme in cholesterol biosynthesis (13). Phenobarbital has been shown to increase the activity of microsomal enzyme in liver biopsy samples (3).

In addition to the direct effects on the enzymes of cholesterol synthesis, phenytoin can alter the synthesis of endogenous substances such as insulin and thyroid hormones, which can affect serum lipid levels. Phenytoin can inhibit insulin secretion (8) and so decrease serum thyroid hormone levels, which might be reflected as a rise in serum cholesterol levels.

Therapy with phenytoin increased the frequency of elevated triglyceride and cholesterol values. The rise in triglyceride level was in some cases very marked but also more short-lived than the change in cholesterol concentration. The increase in serum cholesterol level may therefore be more closely related to the enzyme induction phenomenon than the increase in serum triglyceride concentration.

# ACKNOWLEDGEMENT

The investigation was supported by a grant from the Finnish National Research Council for Medical Science (Finnish Academy of Finland).

## REFERENCES

- Bertels H & Putzki H. Gamma glutamyl transferase and cholesterol during anticonvulsant treatment. *Br Med J* 2: 88, 1975.
- Conney A H. Pharmacological implications of microsomal enzyme induction. *Pharmacol Rev* 33: 333, 1967.
- Coyne M J, Bonorris G G, Goldstein L I & Schoenfeld L J. Effect of phenytoin and phenobarbital on the rate-limiting enzyme of hepatic cholesterol and bile acid synthesis in patients with gallstones. *J Lab Clin Med* 87: 281, 1976.
- Durrington P N, Roberts C J C, Jackson I, Branch R A & Hartog M. Effect of phenobarbital on plasma lipids in normal subjects. *Clin Mol Med* 50: 349, 1976.
- Fallon H J, Lamb R G & Jarman S C. Phosphatidate phosphohydrolase and the regulation of glycerol phospholipid synthesis. *Biochem Soc Trans* (1): 37, 1977.
- Hahn T J, Hendon B A, Scharp B A & Haddad Jr J G. Effect of chronic anticonvulsant therapy on serum 25-hydroxycholesterol levels in adults. *N Engl J Med* 287: 900, 1977.
- Huang T C, Chen C P, Wessler V & Raftery A. A stable reagent for the Liebermann-Burchard reaction: application to rapid serum cholesterol determinations. *Anal Chem* 33: 1405, 1961.
- Kizer J S, Vargas-Cordon M, Brendel K & Bessler R. The in vitro inhibition of insulin secretion by phenylhydantoin. *J Clin Invest* 49: 1947, 1970.
- Lewendahl K & Majum H. Thyroxine and thyrotropin in serum during long-term phenylhydantoin therapy. *Scand J Clin Lab Invest* 36: 141, 1976.
- Molholm-Hansen J, Skovsted L, Brake-Lauridsen U, Kirkegaard C & Sersbæk-Nelsen K. The effect of diphenylhydantoin on thyroid function. *J Clin Endocrinol Metab* 39: 785, 1974.
- Pelkonen R, Fogelholm R & Nikkila E. Increase in serum cholesterol during phenytoin treatment. *Br Med J* 2: 85, 1975.
- Redinger R N & Small D M. The effect of phenobarbital upon bile acid synthesis and pool size, biliary lipid secretion and bile composition. *J Clin Invest* 57: 161, 1973.
- Sperstén M D. Regulation of cholesterol biosynthesis in normal and malignant tissues. In: *Current topics in cellular regulation* vol. 2 (ed B. Horecker & E. Stadtman), pp. 65-100. Academic Press, New York, 1970.
- Wahlefeld A W. Triglycerides. Determination after enzymatic hydrolysis. In: *Methods of enzymatic analysis*, 2nd ed (ed H. U. Bergmeyer), p. 1831. Academic Press, New York and London, 1974.



## BOOK REVIEWS

*Arterial hypertension* WHO Technical Report Series no 628 58 pages Sw fr 6 - WHO Geneva 1978

The WHO series of technical reports also contains a small number of monographs on various interesting clinical topics. The list of the last numbers 590-630 is quite impressive and represents a reference library of great importance for many branches of medicine. There is one possible drawback with this type of publication: the fact that this is a world organization leads to the inclusion of experts selected from as many different countries as possible. In spite of this, the standard of the majority of the experts usually is surprisingly good.

Two of the last reports are of great interest to the internist. No 628 treats one of the greatest and most acute problems in internal medicine: namely the classification, epidemiology and management of hypertension as well as attempts at control of this disease in the population. There is also an "annex" treating antihypertensive agents.

The fact that Professor Gross from Heidelberg has been the chairman is of course a guarantee that the therapeutic side of the problem is well represented. I regard it as a rather serious deficiency that so few references are given. The overwhelming abundance of publications in this field makes it imperative to have a well selected list of publications for reference.

The readers of the *Acta Medica Scandinavica* will note with satisfaction that the Scandinavian investigator Wilhelmsson from Gothenburg has been one of the experts.

Jan G Waldenström

*Immunodeficiency* WHO Technical Report Series no 630 73 pages Sw fr 7 - WHO Geneva 1978

Immunodeficiency is a puzzling condition, especially when it has a genetic background. The fact that many must be involved in the production of immunoglobulin molecules makes it hard to understand how one point on could explain a general decline in the synthesis of a great many different immunoglobulins. The recent findings that the basis may be a mutation in the genes that control the synthesis of one specific enzyme such as adenosine deaminase (ADA) and purine nucleoside phosphorylase (PNP) is easier to understand. These enzymes are obviously necessary for the development of the cells that are involved in immunoglobulin synthesis. These very important facts have only been mentioned very briefly.

Table 1 contains a rather formidable list of primary specific immunodeficiencies. The number is 17, but no 1 contains five subgroups and no 17 two, thus 22 in all. The reader misses references to all the lists of "different processes" that are listed in Tables 1, 2 and 3. To the reviewer it seems clear that a number of these conditions will disappear as independent individuals and possibly others will be added.

On the whole, this brief monograph contains a wealth of facts. There is little room for discussion of problems, but

as a skeleton containing main facts it seems very valuable. The discussion of therapy is competent.

The price is obviously very favourable: it is strongly recommended to the student or needs an overview of the field in its present

Jan G

*The endocrine function of the human* Edited by V T H James M Seno G Martini 612 (628) pages £19.50 Academic and New York 1978

This volume is a record of the papers of the Serrano Symposium held in Florence in October 1976. It contains contributions ranging from steroid and regulation of the adrenal cortex to endocrinology. The clinical part includes endocrine disorders such as hypercorticism, Cushing's disease and congenital adrenal hyperplasia. It also contains discussions on hirsutism and hypertension. The Symposium was to provide a picture of current views and research on a "function". This intention has certainly

been fulfilled. It is impossible to review all the volume of this type. Since the scope is reviewer will also be biased by his own topic. However, it must be stated that the whole is excellent. It provides information throughout and it will also serve as a reference which most libraries would benefit from.

The papers dealing with steroid biosynthesis are very thorough and even include monooxygenase fibres and prostaglandin synthase. Protein binding of steroids, variations of steroids as well as binding presented. Both these sections are very good and provide a good frame for futuristic outlooks.

Congenital adrenal hyperplasia and hirsutism are discussed and the discussion on hirsutism is intriguing. Hypertension with an emphasis on the role of various steroids is discussed in depth, retaining properties of aldosterone and the primary aldosteronism are well presented. The renin-angiotensin system and its effect on the complement presentations of the role of the adrenal cortex in hypertension, saralasin and the interpretation of such data in an excellent way.

Finally, the adrenal function in the fetus, infancy and puberty is presented with a very good of the clinical disorders at the time of puberty.

This volume can certainly be recommended to me great pleasure to give all the contributors an excellent piece of work. I can only wish that they had participated.

John Fredrik Drömling, Västerås

# Immune Complex Glomerulonephritis in Chronic Granulomatous Disease

Case Report of an Eighteen Year Old Girl

D J van Rhenen M I Koolen Th M Feltkamp-Vroom  
and R S Weening

the Department of Medicine Academic Ziekenhuis der Vrije Universiteit the Department of Paediatrics the Department of Clinical Bacteriology and the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service Amsterdam The Netherlands

**ACT** An 18-year-old girl is described who had advanced renal sclerotic lesions probably caused by local focal glomerulonephritis which developed in a Staphylococcus aureus abscess. It is suggested that immune complex glomerulonephritis developed provoked by long term antigenic stimulation of Staphylococcus aureus. The cause of long term bacterial infections was a defect of polymorphonuclear cells to kill bacteria effectively a diagnosis known as chronic granulomatous disease. The girl had intracellularly active antimicrobial drugs but the renal function till no more improvement was necessary.

**KEY WORDS:** chronic granulomatous disease circulating immune complexes local focal glomerulonephritis intracellularly active antimicrobial agents

Acta Med Scand 206 233 1979

The occurrence of immune complex glomerulonephritis has been described not only in patients with bacillary endocarditis but also in patients with other serious infections (3 7 11). We report on a patient who as a result of a disturbance in the function of her polymorphonuclear leukocytes has been exposed to Staphylococcus aureus infection for a long period. Subsequently she developed an immune complex glomerulonephritis. Dysfunction of PMN known as chronic granulomatous disease (CGD) ran a very unusual course because of the patient's late age at onset.

## CASE REPORT

An 18-year-old girl with rapidly progressive renal failure admitted to our hospital for the first time in May 1977. She was the first child of healthy non-consanguineous parents. A 15-year-old sister and a 9-year-old brother are

healthy. The patient had felt physically well since birth when she was admitted to a hospital elsewhere because of slowly resolving pneumonia of the right upper lobe. No bacteria could be isolated. Fibrotic scars were seen at the scars in the top of the right lung. Hepatosplenomegaly was found during this admission. In February 1976 she developed pain in the right upper abdomen. In May 1976 she was admitted with severe abdominal pain. Operation disclosed an overwhelming perforated duodenum by perforation of a liver abscess. Staphylococcus aureus was isolated from the pus. Microscopic hematuria was reported already at this time (Table I).

In January 1977 she was readmitted because hepatomegaly was suspected which could not be confirmed. However, normochromic erythrocytes, protein and hyaline casts were found in the urine. Serum creatinine was 106  $\mu\text{mol/l}$ . No diagnosis was made nor was any treatment given. In April 1977 she was readmitted again for severe abdominal pain. Since her renal function deteriorated rapidly within two weeks she was transferred to our hospital.

On admission the patient looked gravely ill and her temperature was 38.5  $^{\circ}\text{C}$ . Physical examination revealed a palpable mass in the right upper abdomen possibly connected with the liver. Skin pathology was not observed.

## Laboratory data

ESR 81 mm/h WBC  $11.5 \times 10^9/\text{l}$  with 79% morphologically normal PMN 18% lymphocytes and 3% bands. Serum creatinine had quickly risen from 140 to 539  $\mu\text{mol/l}$ . Blood urea 21.4 mmol/l serum protein 87 g/l with 39.4 g/l albumen and 23.6 g/l gammaglobulin. Serum immune electrophoresis showed no paraprotein. Liver functions (aspartate alkaline phosphatase) were normal.

**Abbreviations:** ANF antinuclear factor AU antinuclear body units (Standard Hoechst Behring Werke) CGD chronic granulomatous disease ESR erythrocyte sedimentation rate PAS periodic acid Schiff PMN polymorphonuclear leukocytes WBC white blood cells

**Correspondence address:** D J van Rhenen Academisch Ziekenhuis der Vrije Universiteit de Boelelaan 1117 Amsterdam The Netherlands

Table 1 Summary of laboratory and clinical findings

Date	Serum creatinine ( $\mu\text{mol/l}$ )	Urine sediment	Urinary protein (g/l)	Anti-staphylo-lysine titer (AU)	Details
May 1976	108	Erythrocytes	?		Pertitonitis
Jan 1977	154	Many erythrocytes casts	++		Hepatitis
April 1977	150	Many erythrocytes casts	++		Deterioration of renal function
May 1977	539	Many erythrocytes casts	2.1	100	Admission to our hospital first skin biopsy haemodialysis surgical abscess drainage PMN functional analysis Therapy 80 mg trimethoprim + 400 mg sulfamethoxazole daily
July 1977	Haemodialysis	Few erythrocytes casts	2.2	1	Surgical renal biopsy second skin biopsy
Dec 1977	239	Few erythrocytes	1.9		End of haemodialysis PMN functional analysis
April 1978	308	Few erythrocytes	1.8	1	Relapse third skin biopsy circulating immune complexes demonstrated
June 1978	254	Few erythrocytes	1.2		Therapy rifampicine 600 mg daily Fourth skin biopsy

Many leucocytes erythrocytes granular and hyaline casts were seen in the urine sediment urinary protein was 2.1 g/l. No morphological abnormalities were observed by intravenous pyelography. Liver scintigraphy and echoscopy suggested an intrahepatic process.

The most probable diagnosis was a recurrence of the liver abscess with *Staphylococcus aureus* and the development of immune complex glomerulonephritis. For confirmation of these possibilities the following investigations were performed: Antistaphylo-lysine titer: 100 AU (normal value <0.5). Complement  $\text{CH}_{50}$  86 U/ml (lower normal limit 50). No indications for diffuse intravascular coagulation were found. ANF negative. Latex fixation test positive. Immunoelectrophoresis of the urine showed an aspecific proteinuria.

A summary of the laboratory and clinical findings is given in Table 1.

#### Histo- and immunopathological investigations

**Skin biopsies.** The first punch biopsy was taken from the normal skin of the extensor side of the forearm one day after admission. Immunofluorescence studies revealed fine granular material in the capillary walls of the papillary dermis positive for IgA and fibrinogen, less extensively also for IgM and C3/4. The second biopsy taken two months after admission revealed no deposits. The third biopsy taken during relapse showed granular material in the capillary walls of papillary dermis positive for IgM, IgG and C3/4. C1q was not found. The fourth biopsy showed no abnormalities. The skin biopsies were studied by Dr C. Nieboer, Department of Dermatology, AZVU.

**Surgical renal biopsy** (performed two months after admission because of the patient's poor condition). The re-

nal biopsy was divided in two parts: one for fixation in formalin and the other for freezing in liquid nitrogen. The fixed tissue was routinely embedded in paraplast cut and stained with haematoxylin and eosin, periodic acid silver methenol and periodic acid Schiff (PAS). The frozen tissue was embedded in a cryostat and studied for the presence of IgM, IgE, fibrinogen, C1q and C3.

By light microscopy 16 of the 30 glomeruli showed moderate to advanced sclerosis (Fig. 1). In 10 of the 30 glomeruli showed definite local focal with lobular condensation, capsular adhesions and crescent formation (Fig. 2). About 5 glomeruli were normal with only slight endothelial swelling. The



Fig. 1 PASM/Azan stain showing glomeruli with advanced sclerosis.



Fig 2 Staining showing glomeruli with capsular adhesion, crescent formation and sclerosis

was increased locally due to fibrosis and/or by lymphocytes and histiocytes. Tubular structures were seen in the fibrotic areas and fibrillar casts in the medulla. Fluorescence revealed no deposits of immunoglobulin in the glomeruli. Some patchy IgG and C3 were present in the walls of the small vessels. There were advanced renal sclerotic lesions and local focal glomerulonephritis.

#### Functional capacity of phagocytic cells

Effects in resistance against bacterial infections and functional tests were performed on PMNs. Studying the functional capacities of the cells, a normal chemotactic responsiveness as well as the leading front method (16) and casein tractant (65  $\mu$ m (mean  $\pm$  S.D. in 31 normal controls) (15). The uptake of  $^{14}$ C labelled Staphylococcus was measured essentially as described by (14). In this assay lysostaphin is used to lyse and other non-phagocytized bacteria. The patient's PMNs phagocytized these bacteria even better than the control cells (1.14  $\pm$  0.34% (mean  $\pm$  S.D.  $n=70$ )). The patient's PMNs were unable to kill these bacteria within 60 min as judged by an assay as described by Solberg (13) (Fig 3).

Use of this defect in intracellular killing was the first stimulation of the oxidative reactions known to be important for the killing of bacteria. During phagocytosis a 20-fold increase in oxygen consumption is observed (15). The consumed oxygen is probably by an NADPH oxidase to superoxide. These radicals dismutate spontaneously or by superoxide dismutase to hydrogen peroxide. Bacteria dal properties. The patient's PMNs however failed to show the normal burst. Oxygen consumption (0.3 nmoles  $O_2$ /min) was hardly stimulated during phagocytosis (S.D. in 20 normal controls 4.2  $\pm$  1.3). As a result

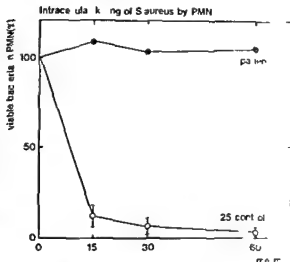


Fig 3 Intracellular killing capacity by polymorphonuclear leukocytes (mean  $\pm$  S.D.)

no stimulation of superoxide radical production (not shown) and hydrogen peroxide formation was observed (Fig 4). These abnormalities were confirmed on two occasions. Moreover, the monocytes also failed to produce hydrogen peroxide during ingestion of zymosan (not shown). Activities of the enzymes glucose-6-phosphate dehydrogenase, 6-phospho-glucanate dehydrogenase, glutathione peroxidase and glutathione reductase in the PMNs were all normal.

We concluded therefore that this patient suffered from CGD. Family studies failed to detect carriers of this disease in a normal finding in female CGD patients (9).

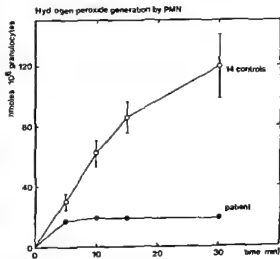


Fig 4 Hydrogen peroxide generation by polymorphonuclear leukocytes (mean  $\pm$  S.D.)

Table 1 Reported cases of gangrene of the tongue in temporal arteritis

	Age (y)	Sex	Histological examination
Bergan (1) (Horton (10))	80	♀	Not performed
Howard & Cremin (11) (Wise (18))	74	♀	Not performed
Brearley & MacDonald (3)	82	♀	Arteritis temporalis
McGill (13)	77	♀	No information
Pitt et al. (14)	78	♀	Organized thrombosis without giant cells
Reed & Inglis (16) (Horton (10))	72	♀	No information
Kinmont & McCallum (12)			
Davis & Davis (4)	81	♀	Giant cell arteritis
Present study	69	♀	Arteritis temporalis (giant cell arteritis)

Horton (10) did not observe any case of gangrene among his 200 patients. Kinmont and McCallum (12) reported that 7 of their 59 patients with giant cell arteritis had varying degrees of glossitis rarely followed by gangrene. That gangrene of the tongue is so rare may be due to the rich blood supply with anastomoses of the artery branches whereas the frequent ocular involvement in temporal arteritis (2) probably is due to the fact that the retinal artery is an end artery. Gangrene of the tongue has been reported in at least 9 patients with suspected or histologically verified temporal arteritis (Table 1). Pain in the jaw muscles (10) and even the tongue (8) is often seen and may be explained by reduction of blood supply in the acute stage of the disease.

As the necroses indicate a bilateral arterial involvement it seems unlikely that the unilateral mechanical intervention (arterial biopsy in local anesthesia) might have precipitated the symptoms. On the other hand manipulation of the artery may have resulted in retrograde spasm or thrombosis caused a reduction of the blood flow to a level below the critical resulting in ischemic necroses. Regression of symptoms after biopsy has not been described in the literature but Profant (15) reported progression of symptoms after extraction of teeth.

Negative biopsies are rather frequent (17). In these cases the diagnoses of temporal arteritis or polymyalgia rheumatica are based on clinical symptoms and blood tests, and corticosteroid treatment is started. It is agreed that immediate steroid treatment is indicated in case of eye involvement (2). To avoid further progression and such sudden complications as the above mentioned we would like to suggest that all patients should be treated with steroids before biopsy if they are strongly suspected of having temporal arteritis or polymyalgia rheumatica. The possibility of obtaining a

positive biopsy during or after steroid treatment does not seem to be diminished by this procedure (5, 6).

## REFERENCES

- 1 Bergan J J Ischemic necrosis of the tongue. *Bull North Univ Med School* 33: 38, 1949.
- 2 Birkhead N C, Wagoner H P & Shulman R E Treatment of temporal arteritis with adrenocorticosteroids. *JAMA* 163: 821, 1957.
- 3 Brearley B F & MacDonald J G Giant cell arteritis resulting in infected gangrene of the tongue. *Med J* 115: 1151, 1961.
- 4 Davis A E & Davis T P Gangrene of the tongue caused by temporal arteritis. *Med J Aust* 2: 4, 1961.
- 5 Fauchald P, Rygvold O & Oestbye B Giant cell arteritis and polymyalgia rheumatica. Circulation biopsy findings. *Ann Intern Med* 77: 841, 1972.
- 6 Hamann B Polymyalgia arteritica. *Acta Med (Suppl)* 533, 1972.
- 7 Harris M Dissecting aneurysm of the aorta. *Br Heart J* 30: 840, 1968.
- 8 Henderson A H Tongue pain with giant cell arteritis. *Br Med J* 4: 337, 1967.
- 9 Hutch J M Dermatologic manifestations of giant cell arteritis. *Arch Dermatol* 101: 409, 1970.
- 10 Horton B T Complications of temporal arteritis. *Br Med J* 1: 105, 1966.
- 11 Howard S & Cremin M D Acute parenchymatous glossitis with gangrene of the tongue. *Lancet* 1959.
- 12 Kinmont P D C & McCallum D I The pathology and course of giant-cell arteritis. *Dermatol* 77: 193, 1965.
- 13 McGill R J Gangrene of the tongue. *Br Med J* 1: 1610, 1961.
- 14 Pitt P, Wallace J & MacGregor G A Giant cell arteritis. *Br Med J* 1: 1394, 1961.
- 15 Profant H J Temporal arteritis. *Ann Otol Laryngol* 1: 308, 1944.
- 16 Reed C & Inglis M J Acute massive gangrene of the tongue. *Br Med J* 2: 575, 1965.
- 17 Soelberg Sorensen P & Lorenzen I Giant cell arteritis temporal arteritis and polymyalgia rheumatica. *Acta Med Scand* 201: 207, 1977.
- 18 Wise D Acute parenchymatous glossitis with gangrene of the tongue. *Lancet* 2: 674, 1969.

## Drug Induced Neutropenias in the Stockholm Region 1976-1977

Per Arneborn and Jan Palmblad

From the Department of Infectious Diseases, Roslagstulls Hospital and Department of Medicine, Södersjukhuset, the Karolinska Institute, Stockholm, Sweden

**OBJECT** Previously we reviewed the incidence of drug induced neutropenia in the Stockholm region during the years 1973-75. We here present an equivalent study for the years 1976-77. The incidence of drug induced neutropenia excluded remained around 0.01%. About 70% of the cases were caused by sulphonamides, the other causes: antithyroid drugs and flucanazones were most frequent. The mortality was 27% in contrast to only 2% in our previous study. Of the seven patients who died, 5 had taken amides.

**KEY WORDS** agranulocytosis, drugs—adverse reactions. Acta Med Scand 706 741-1979.

In our previous paper we reviewed the incidence and of drug induced neutropenia in the Stockholm region between 1973 and 1975 (1). We also found that only approximately 40% of the cases had been reported to the Swedish Adverse Drug Reaction Committee. Due to this fact and also because new drugs are introduced continuously, we felt it important to undertake regular follow-up. We present a study comprising the Stockholm region during the years 1976 and 1977.

## METHODS

The methods have been detailed previously (1). The records of patients discharged with a diagnosis of agranulocytosis (1967 ICD classification 99.0) during the years 1976-1977 were obtained from the Stockholm County Council Public Health Board Information System. The records were reviewed for the presence of neutropenia (reflected as blood neutrophil count  $<1.0 \times 10^9/l$ ) during hospital stay, sex and age of the patient, intake of drugs preceding the development of neutropenia, other possible co-existing diseases, a detailed presentation of infections and the general outcome. Neutropenia was classified as drug induced if it was known to cause neutropenia had been taken, or if it followed its withdrawal (the patient surviving the withdrawal phase) and no other diseases associated with neutropenia were present.

Drug induced neutropenias were further divided into three groups depending on whether the patients had taken only one drug (group I), more than one probable drug (group II) or drugs causing a dose-dependent neutropenia (cytostatics). The latter group is not considered in the following discussion.

## RESULTS

During the years 1976-77 93 patients had been discharged with the diagnosis of agranulocytosis. The records of three patients were not found. Eight pa-

**Additional data on the 27 cases of drug induced neutropenia (groups I+II)**

One patient counted as one in the sum, was admitted once in 1976 and once in 1977 because of chronic neutropenia to be caused by penicillin.

No of cases	Days of hospital stay (mean)	Males			Females			Fatal cases
		N	Age (y)		N	Age (y)		
			Mean	Range		Mean	Range	
16	17.6	4	45.5	8-68	17	50.9	17-68	3
17	17.5	5	71.8	51-83	7	66.0	48-76	4
27	17.6	9	61.7	8-83	18	56.5	17-76	7

Table II Drugs involved in 27 cases of drug induced neutropenia. Fatal cases are given in parentheses

Group I=patients who had taken only one drug group II=patients who had taken two or more drugs (all possible neutropenia-causing drugs being listed). Swedish synonyms at present on the market are given in parentheses

	Group I	Group II
Sulphonamides	11	2
Various	9 (3)	1
Salicylazosulphapyridine (Salazopyrin <sup>®</sup> )		
Trimethoprim-sulfamethoxazole (Bactrim <sup>®</sup> Eusaprim <sup>®</sup> Trimetoprim-sulfa <sup>®</sup> )		1 (1)
Antithyroid drugs	2	
Propylthiouracil (Tiotil <sup>®</sup> )	1	
Thiamazole (Thiagazole <sup>®</sup> )	1	
Phenothiazines	1	2
Unspecified	1 (1)	
Trifluoperazine (Terfluzin <sup>®</sup> )		1
Chlorpromazine (Hibernal <sup>®</sup> )		
Largactil <sup>®</sup> Klorpromex <sup>®</sup> )		1 (1)
Diuretics	1	
Hydrochlorothiazide (Dichlotride <sup>®</sup> )		
Esidrex <sup>®</sup> Dopamet comp <sup>®</sup>		
Hydromet <sup>®</sup> Moduretic <sup>®</sup> )	1	
Antibiotics		3
Amoxicillin (Imacilin <sup>®</sup> )		
Bristamox <sup>®</sup> )		1
Ampicillin (Doktacilin <sup>®</sup> )		
Pentrexyl <sup>®</sup> )		1 (1)
Gentamicin (Garamycina <sup>®</sup> )		1 (1)
Antiphlogistics	1	
Indomethacin (Indomee <sup>®</sup> )		
Confortid <sup>®</sup> )	1	
Miscellaneous	6	6
Unspecified Italian purgative	1	
Penicillamine <sup>®</sup> (Cuprimine <sup>®</sup> )		
Penicillamine <sup>®</sup> )	1	
Phenytol (Diphydan <sup>®</sup> Epanutin <sup>®</sup> )		
nantoin <sup>®</sup> Lehydan <sup>®</sup> )	2	
ipramin (Anafranil <sup>®</sup> )		1
nidine (Cardioquin <sup>®</sup> Kinidin <sup>®</sup> )		
nytal <sup>®</sup> )		1
Ietamizole (Noramidopyrin)	1	
Tolbutamide (Artosin <sup>®</sup> )		
Rastinon <sup>®</sup> )	1	
Phenemal (Included in 15 different pharmaceutical specialties on the Swedish market)		1
Chlormezanone (Lotac <sup>®</sup> Tranecopal <sup>®</sup> Trancoprin <sup>®</sup> )		1
Paracetamol (Included in 17 different pharmaceutical specialties)		1
Multiple drugs <sup>a</sup>		1

The patient has a chronic neutropenia thought to be caused by penicillamine

<sup>a</sup> The patient had got at least 18 different drugs. Many of them can cause neutropenia

<sup>c</sup> The patient had taken 4 possible drugs

Table III Infections noted in the records

Some patients had signs of more than one

Septicaemia	4
Tonsillitis pharyngitis (necrotizing tonsillitis 1)	10
Pneumonia	3
Gastroenteritis	2
Miscellaneous	4
Fever of unknown origin	5
No signs of infection	5

tients did not fulfil the criterion of having  $1 \times 10^6$  neutrophils/l. Of the remaining 25 had neutropenia caused by drugs the above mentioned definitions. Of these one has had 2 episodes of neutropenia different drugs and is therefore counted in the calculation of incidence 1 episode altogether. In addition to these one patient has a chronic neutropenia to be caused by penicillamine. She is mentioned in our earlier paper (1) and does not repeat the case.

Of the other 46 cases 23 were caused by statics 12 were due to a primary haematological disease and 11 to some other disease. It could not be decided whether the neutropenia was due to drug or disease. In 9 cases the neutropenia remained unknown.

Based on the 26 new episodes of drug induced neutropenia presented here the mean incidence during these two years is estimated to be 0.009% (approximately 1500 000 inhabitants in the Stockholm region). Seven (27%) of them died of complications to the neutropenia.

Table I gives further characteristics of the drug induced cases. Table II lists the various drugs involved and Table III the infections described in the records.

## DISCUSSION

The pattern of drugs causing drug induced neutropenia in this study resembles earlier findings in most other studies (2, 3, 4, 6). Thus various sulphonamide drugs were among the most commonly noted causes of drug induced neutropenia.

It is noteworthy that we still have not found that metimazole caused neutropenia although

drawn from the Swedish market in 1973  
 with metamizole neutropenia had taken  
 the drug bought abroad  
 annual incidence of drug-induced neutro-  
 penia study (0.009%) is similar to that in  
 our study (0.01%) (1). These figures are  
 far to the findings in earlier Swedish  
 from other parts of the country during the  
 1960s (2-4).

Mortality figure of 27% closely resembles  
 that of other investigations from recent years  
 is much higher than the rate we found in  
 our study (7%) based on a 3-year survey.  
 The reason for this discrepancy it-  
 emizes the potentially serious nature of drug-  
 induced neutropenia.

In seven fatal cases five had taken sul-  
 phonamides in one case together with other  
 drugs. Perhaps this just reflects the wide  
 use of sulphonamides. The use is expected  
 to decrease further in the near future due to the  
 introduction of new sulphonamide-containing  
 preparations. One is trimethoprim  
 cotrimazole. Another is Fan-

sidar® (sulphadoxine pyrimethamine) which  
 is now recommended by the WHO for prophylaxis  
 against chloroquine-resistant malaria (5, 7). The  
 serum half-life for sulphadoxine is about 10  
 approximately 200 hours which hypothetically  
 could cause a prolonged and thus more severe  
 neutropenia.

## REFERENCES

1. Arneborn P & Palmblad J. Drug-induced  
 neutropenia in the Stockholm region 1973-75. Inci-  
 dence and causes. *Acta Med Scand* 234: 283, 1978.
2. Bottiger L E & Westholm B. Drug-induced  
 dyscrasias in Sweden. *Br Med J* 3: 339, 1973.
3. Piscotta A V. Immune and toxic mechanisms in  
 drug-induced agranulocytosis. *Semin Hematol* 10: 273,  
 1973.
4. Westholm B & Rezenstein P. Drug-induced  
 agranulocytosis. *Proc 17th Meeting of the Society  
 Drug Toxicology Excerpta Med Int Congr Series* 22: 217,  
 1970.
5. WHO Weekly Epidemiol Rec 25: 181, 1978.
6. Williams W J, Bentler L P, Friesen A J & Runfey  
 R W. Hematology. McGraw Hill, New York, 1972.
7. US Public Health Center for Disease Control. Morbidity  
 and mortality. *Weekly Report* 27: 84, 1978.



# The very journals for you!

## **Acta Chirurgica Scandinavica**

Editor L. Thoren  
8 issues per volume. Free supplements. Including free subscriptions to the *Scandinavian Journal of Plastic and Reconstructive Surgery* (without suppl.) the *Scandinavian Journal of Thoracic and Cardiovascular Surgery* (without suppl.) and the *Scandinavian Journal of Urology and Nephrology* (without suppl.) Together 17 issues per year.  
Current volume 145/1979  
Sw. kr 470 per year incl postage

## **Acta Dermato Venereologica**

Editor Nils Thyresson  
6 issues per volume. Free supplements.  
Current volume 59/1979  
Sw. kr 190 per year incl postage

## **Acta Medica Scandinavica**

Editor J. Waldenström  
6 issues per volume. Free supplements.  
Current volumes 205-206 1979  
Sw. kr 375 per year (two volumes) incl postage

## **Acta Oto Laryngologica**

Editor C. A. Hamberger  
6 issues per volume. Free supplements.  
Current volumes 87-88 1979  
Sw. kr 300 per year (two volumes) incl postage

## **Acta Pædiatrica Scandinavica**

Editor R. Zetterström  
6 issues per volume. Free supplements.  
Current volume 68 1979  
Sw. kr 300 per year incl postage

## **Audiology**

Editor Stig Arlinger  
4 issues per volume. Free supplements.  
Current volume 8 1979  
Sw. kr 175 per year incl postage

## **Scandinavian Journal of Infectious Diseases**

Editors Justus Ström and Sten W. Nöblad  
4 issues per volume. Free supplements.  
Current volume 11/1979  
Sw. kr 175 per year incl postage

## **Scandinavian Journal of Plastic and Reconstructive Surgery**

Editor Bengt Johanson  
3 issues per volume. Free supplements.  
Current volume 13/1979  
Sw. kr 185 per year incl postage

## **Scandinavian Journal of Psychology**

Editor Lars Hebbon  
4 issues per volume.  
Current volume 20 1979  
Sw. kr 170 per year incl postage

## **Scandinavian Journal of Rehabilitation Medicine**

Editor Olle Hook  
4 issues per volume. Free supplements.  
Current volume 11/1979  
Sw. kr 140 per year incl postage

## **Scandinavian Journal of Rheumatology**

Editor Veikko Lahti  
4 issues per volume. Free supplements.  
Current volume 8 1979  
Sw. kr 140 per year incl postage

## **Scandinavian Journal of Social Medicine**

Editor Ragnar Berglund  
3 issues per volume. Free supplements.  
Current volume 7 1979  
Sw. kr 140 per year incl postage

## **Scandinavian Journal of Thoracic and Cardiovascular Surgery**

Editor Viking Olov Björk  
3 issues per volume. Free supplements.  
Current volume 13 1979  
Sw. kr 185 per year incl postage

## **Scandinavian Journal of Urology and Nephrology**

Editor Åke Friberg  
3 issues per volume. Free supplements.  
Current volume 13 1979  
Sw. kr 185 per year incl postage

## **Uppsala Journal of Medical Sciences**

Editor Gunnar Agren  
3 issues per volume. Free supplements.  
Current volume 84 1979  
Sw. kr 100 per year incl postage

Swedish subscribers: Add VAT to all prices

Free inspection copies on request—write to

**The Almqvist & Wiksell Periodical**  
Box 62, S-101 20 Stockholm, S

# Procainamide-Induced Lupus Erythematosus-like Syndrome in Relation to Acetylator Phenotype and Plasma Levels of Procainamide

C Sonnhag, E Karlsson and J Hed

From the Departments of Internal Medicine (Division of Cardiology), Clinical Pharmacology, and Medical Microbiology (Clinical Immunology Unit), University of Linköping, Linköping, Sweden

**ACT** To investigate the relationship between phenotype and the development of procainamide (PA) induced systemic lupus erythematosus (SLE) like syndrome 28 patients with chronic atrial arrhythmias treated with PA were followed for one year. The therapy was guided by monitoring in all patients in order to obtain a proposed therapeutic plasma level of PA. Patients (30%) both slow and rapid acetylators developed the SLE-like syndrome within one year. Plasma levels were similar in both slow and rapid acetylators and there was no difference in total dose at the end of therapy before development of the syndrome. Thus the acetylator phenotype is probably of minor predictive importance when PA therapy is guided by plasma monitoring. On the other hand the antinuclear antibodies appeared significantly more rapidly in patients developing the syndrome and could possibly be used as an indicator of risk. The results support the hypothesis that the primary amino group structure of PA may be of importance in the induction of the SLE-like syndrome.

**Antinuclear antibodies, acetylator phenotype, procainamide, N acetylprocainamide, procainamide, lupus erythematosus.**

Acta Med Scand 206 245 1979

Procainamide (PA) has been reported to induce a lupus erythematosus (SLE) like syndrome during long term therapy but hydralazine and procainamide (PA) have been implicated most frequently (1, 4, 14, 19, 25). Both drugs have also been reported to be polymorphically acetylated in man (2, 3, 29) and the syndrome seems to occur more frequently in slow than rapid acetylators (14, 29).

A primary amino group is common to most of the drugs causing the syndrome and has been suggested as the responsible factor (7, 22). Campbell et al (5) also found a correlation between acetylator phenotype and PA plasma levels: for a given daily dose of PA, slow acetylators had a higher mean PA plasma level than rapid acetylators. However, if the therapy is guided by plasma monitoring, rapid and slow acetylators will probably reach the same PA plasma level and the acetylator phenotype would be of minor importance for the risk of inducing the SLE like syndrome.

Earlier studies on the frequency of the SLE like syndrome during PA therapy have focused on the importance of the dose and acetylator phenotype. The purpose of this study was to evaluate the importance of the plasma levels of unchanged PA and the metabolite N acetylprocainamide (NAPA) for the development of the syndrome.

## PATIENTS AND METHODS

Long term therapy with PA was initiated in 40 patients with ventricular arrhythmia as motivating treatment. Some clinical characteristics of the patients are given in Table I. The majority had a previous history of coronary artery disease and were treated concomitantly with other drugs not known to induce the SLE like syndrome. All patients gave the informed consent to participate in the study.

### Laboratory checks

Prior to the start of therapy and every second month thereafter the following parameters were checked: ESR,

**Abbreviations:** SLE, systemic lupus erythematosus; PA, procainamide; INH, isoniazid; NAPA, N acetylprocainamide; ANA, antinuclear antibodies; FITC, fluorescein isothiocyanate; DNA, deoxyribonucleic acid;  $T_{1/2}$ , plasma half life.

Table 1 Clinical characteristics of the initial 40 patients

Age (y)	
Mean	62
Range	28-82
Females	12
Males	28
Diagnosis	
Coronary heart disease	26
Others	14
Concomitant therapy	
Digitalis	18
Diuretics	17
$\beta$ -adrenergic blocking drugs	22
Others	15
None	6

Hb antinuclear antibodies (ANA) serum electrophoresis. The concentrations of PA and NAPA at both minimum and expected maximum plasma level were determined and the dose was adjusted in order to attain a PA plasma level within the proposed "therapeutic" range of 4-8  $\mu\text{g/ml}$  (17) in all patients. At every check-up the patients underwent a thorough clinical examination and were questioned about SLE symptoms. The plan was to follow all patients for 12 months or until symptomatic adverse reactions arose. Thus PA therapy was not discontinued due to a raised ANA titer alone.

#### Criteria of the SLE-like syndrome

The following criteria were required for the diagnosis of PA-induced SLE like syndrome: A significantly raised ANA titer with at least one of the following symptoms or signs: arthralgia, arthritis, myalgia, pericarditis, pleuritis, pulmonary infiltration, fever. These symptoms and signs had also to diminish or disappear after withdrawal of PA therapy.

#### ANA determination

Unfixed 5  $\mu$  cryostat sections of mouse kidney and liver were used as substrate to detect against tissue constituents by indirect fluorescence technique (6). The sera dilution of 1:25 for antibodies of the IgG class, the appropriate fluorescein isothiocyanate (FITC) conjugated antiserum (Wellcome) used at overnight. Fluorescence titre was established with microtitre (1:25, 1:100, 1:400 etc.) until an endpoint was reached. Sera with ANA were tested for antibodies to deoxyribonucleic acid (DNA) using the microtitre test with the kinetoplast of *Critidia lucifera* as substrate (the Central Laboratory of the Swedish Cross Blood Transfusion Service). Titres of either IgG or IgM were regarded as significant.

#### Determination of acetylator phenotype

The acetylator phenotype of each patient was determined either by the INH test (37 patients) or by the pyridine test (3 patients).

The INH test was performed by giving the patient a single oral dose approximately 10 mg/kg (Tibinale<sup>®</sup>). Food intake was not allowed 2 hours later. Venous blood samples were taken from heparinized tubes before and 3, 5, 7 and 9 hours after INH dose. The plasma was frozen until analysis according to the method described by Maher et al. (8). Plasma half-life ( $T_{1/2}$ ) and the overall elimination constant ( $k$ ) were calculated from the regression line representing the logarithmic decay of the concentration. Patients with  $T_{1/2}$  longer than 2.1 hours were classified as slow acetylators according to Hays (12).

The sulphapyridine test was performed in the following way. The fasting patient was given 400 mg pyridine (Septipulmon<sup>®</sup>) and food intake was not allowed 2 hours later according to Schroder and Evans (9). Specimens collected between the 7th and 8th hours

#### II Other reasons than SLE manifestations for discontinuing PA therapy in 12 patients

slow acetylator R=rapid acetylator w=weeks m=months

Sex	Acetylator phenotype	Reason for withdrawing PA	Time of withdrawal of PA	ANA titer at withdrawal
♂	S	Urticaria	3 w	Neg.
♂	R	Urticaria	3 w	Neg.
♀	S	Urticaria	3 m	1/100
♂	R	Hypotension + vertigo	2 w	Data missing
♀	R	Suspected asthma bronchiale	2 m	Neg.
♂	S	Voluntarily no side-effects	2 m	Neg.
♂	S	Voluntarily no side-effects	9 m	Neg.
♀	S	Voluntarily no side-effects	2 m	1/200
♂	S	Voluntarily no side-effects	5 m	1/400
♂	S	Death from left heart failure	5 m	Neg.
♂	S	By mistake because of raised ANA titer	4 m	1/400
♂	S	Therapeutic failure with left heart failure and aggravated arrhythmias	8 m	1/100

## II Characteristics of 28 patients with (group A) without (group B) SLE manifestations

	Group A (n=9)	Group B (n=19)
Age	59 47-70	63 28-75
Sex	4 5	5 14
Major phenotype	7 2	17 2
Impaired renal function creatinine >1.3 mg/100 115 µmol/l	1	6
Pre-existing heart disease	7 2	11 8
Concomitant therapy		
Diuretics	5	10
Anticancer drugs	3	9
Sedative blocking drugs	4	6
Others	1	4
PA dose (g)		
Initial	646	1156
Maintenance	135-1620	540-1620
PA plasma level (mean ± SD)		
Initial	4.6 ± 1.8	4.0 ± 1.4
Maintenance	6.7 ± 2.2 <sup>a</sup>	5.9 ± 1.9
5-NAPA plasma level (mean ± SD)		
Initial	3.4 ± 1.3 <sup>b</sup>	4.9 ± 3.5
Maintenance	3.4 ± 1.7	5.4 ± 3.0 <sup>d</sup>

<sup>a</sup>n=6 <sup>b</sup>n=4 <sup>c</sup>n=18

<sup>a</sup> were analysed according to the method of Hansson and Berg (13)

<sup>b</sup> was an analysis of plasma concentration of PA and 5-NAPA samples for determination of plasma levels of the drug were centrifuged and stored frozen until analysed. The sample was analysed simultaneously for PA and 5-NAPA by a sensitive liquid chromatography method according to Graffner et al. (11)

## RESULTS

Of the three patients were classified as slow and 7 as rapid acetylators. In 12 patients the therapy was continued for reasons other than development of SLE like syndrome (Table II). The immunologic status of these patients at the time of withdrawal of PA is also shown. Characteristics of the remaining 28 patients, 4 of whom were rapid and

24 slow acetylators are given in Table III. Nineteen continued the therapy without side effects (group B).

## SLE like syndrome

Nine of the 28 patients, 2 rapid and 7 slow acetylators, developed clinical manifestations of the SLE like syndrome (group A). The signs and symptoms indicating the syndrome are given in Table IV. The earliest and most common symptom was migratory and symmetrical arthralgia. The ESR was higher than the pretreatment value in only 2 patients. No systematic abnormalities in the serum electrophoresis pattern and no other haematological or renal disturbances were recorded.

Fig. 1 shows the development of the SLE like syndrome with time. It occurred less than 4 months after initiation of the PA treatment in 5 of the 9 patients, one patient—a rapid acetylator—presenting typical manifestations within only 1 month. After discontinuation of the PA therapy the signs of the syndrome disappeared in all patients. In most of them the symptoms improved rapidly, but one patient required steroid therapy for 2 months. The ANA titers returned slowly to normal and were 1/100 or less in 6 of the 7 patients who could be followed for 10 months.

## ANA titer

Fig. 2 shows the time needed for the development of a significantly raised ANA titer (either IgG or IgM ≥ 1/100) after initiation of the PA therapy. The ANA titer increased significantly earlier in group A than in group B ( $p < 0.01$  at 2 months,  $p < 0.05$  at 4 and 8 months, Fisher's exact probability test).

ANA titers at the onset of SLE manifestations in group A patients and after 12 months of PA therapy in group B patients are given in Fig. 3. Patients with the SLE like syndrome had higher titers (≥ 1/400) than patients without. In 12 of the 19 patients in

Table IV Dominant clinical manifestations in 9 patients developing the SLE like syndrome

	No. of patients
Arthralgia	8
Arthritis	2
Pleuritis	2
Pulmonary infiltration	1
Pericarditis	1

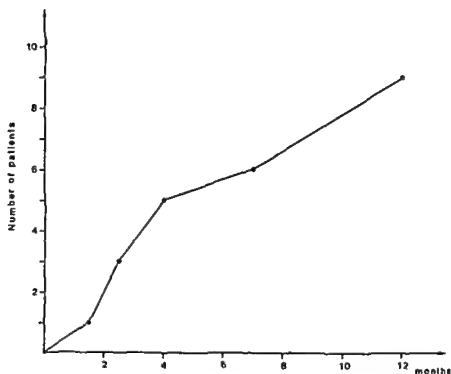


Fig 1 Time to development of clinical manifestations in patients with PA and SLE-like syndrome

group B the ANA titer was significantly raised. Consequently 7 patients (25%) could be treated with PA for one year or longer without any significant influence on the ANA titer.

Sera from all 9 patients in group A and from the 8 in group B who developed the highest ANA titers

were examined for DNA antibodies. All were negative.

#### Plasma levels of PA and NAPA

The total intake of PA and the plasma levels of PA and NAPA are given in Table III. The

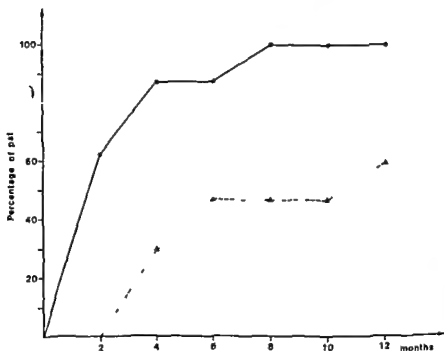


Fig 2 Time to development of a significantly raised ANA titer ( $\geq 1/100$ ) in 8 patients (—) and 17 patients (---). Some missing for 1 patient in A and 2 patients in B.

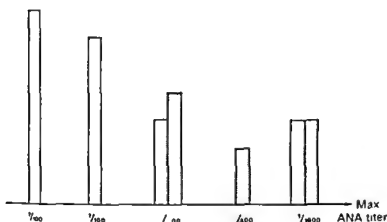


Fig 3 ANA titers at manifestation of symptoms in group A patients (□) and after one year's treatment in group B patients (■)

of PA in group B was about twice that in group A. The plasma levels of PA were somewhat lower and those of NAPA lower in patients in group A than in group B though the differences are statistically significant. In both groups the mean concentration of PA was within the proposed therapeutic range (17). Table V shows plasma levels of PA and NAPA in rapid and slow acetylators. PA plasma levels were the same in slow and rapid acetylators while NAPA plasma levels were somewhat higher in the rapid acetylators. This could be expected as NAPA is an active metabolite of PA.

## DISCUSSION

In our study 9 (30%) out of 28 patients developed SLE like syndrome during one year on PA treatment. This is in good accordance with the frequency found in other similar studies (3, 14, 19). On the other hand the finding by Henningsen et al. that slow acetylators are more prone to develop SLE like syndrome than rapid acetylators seems less valid in our study. Admittedly the study population was small but the rapid acetylator phenotype is stable with the development of this side effect. The therapy was guided by PA plasma concentrations in all our patients. The standard dosage recommended by Henningsen et al. was much lower (1-2 g/day) than ours (mean 3.2 g/day). Consequently plasma concentrations were probably higher

in our patients. In most cases they reached the proposed therapeutic plasma range (17). Also with an individually tailored dosage the PA plasma concentration reaches the same level in slow and rapid acetylators. Therefore if the free amino group of the PA molecule is responsible for the SLE like syndrome it is logical that the frequency of the syndrome is the same in patients of slow and rapid acetylator phenotype.

Healthy subjects are reported to break down procainamide evenly into slow and rapid acetylators (15, 29). The pronounced predominance of slow acetylators in the present series is difficult to explain. However the same uneven distribution of phenotypes has been reported for other groups of patients with various diseases such as spontaneous SLE (20, 28), tuberculosis (12), acute myocardial infarction (16) and renal diseases (24). It is conceivable that the

Table V Steady state plasma levels of PA and NAPA (mean and range) in slow and rapid acetylators

	Slow acetylators			Rapid acetylators		
	Mean	Range	n	Mean	Range	n
PA (µg/ml)						
Max	6.0	2.6-10.0	22	6.2	4.0-7.5	3
Min	4.1	1.6-6.9	24	4.7	2.9-5.7	3
NAPA (µg/ml)						
Max	4.9	1.9-12.5	20	6.6	5.9-7.2	2
Min	4.4	1.2-13.5	23	6.1	5.8-6.4	2

slow acetylator phenotype reflects a genetic pre disposition for a number of diseases

ANA titers rose significantly more rapidly and reached higher levels in group A than in group B. Seven of the 28 patients could be treated with PA for one year without developing a significant positive ANA titer. In comparison, Kosowsky et al (19) and Henningsen et al (14) found negative ANA titers in 0 and 17% respectively after one year of PA therapy.

Despite highly positive ANA titers, the sera from patients with a PA induced SLE like syndrome did not contain antibodies to native DNA. This finding is in accordance with those of Blomgren et al (3) and Koffler et al (18). The presence of antibodies to native DNA and consumption of complement are considered to be the best indicators of activity in SLE. Neither of them have been demonstrated in PA induced SLE, but are usually seen in spontaneous SLE (3). This difference may perhaps explain the milder nature of the drug induced SLE. Renal changes have, however, been described in a few patients with PA induced SLE, in whom PA therapy could not be discontinued (21-31). The milder nature of the drug induced SLE is therefore possibly explained by the prompt withdrawal of the responsible agent.

According to Kosowsky et al (19), SLE like manifestations are rarely seen during the first 3 months of PA therapy. However, it is obvious from our data that with a higher dosage, clinical symptoms of SLE can develop earlier. Thus, 3 of the 9 patients with SLE manifestations presented with fulminant symptoms after only 1.5-2.5 months of

In contrast to earlier reports (14-32), we found no relationship between either the duration of PA therapy or the total PA dose and the development of ANA or the SLE like syndrome. Thus, the mean duration of PA therapy before development of the syndrome was 6.8 months in rapid acetylators against 6.3 months in slow acetylators. A probable reason for these findings is that we adjusted the PA dosage in all patients in order to reach the proposed therapeutic plasma level. In agreement with Campbell et al (5), we then found that the mean daily dose of PA was higher in rapid (3.6 g) than in slow acetylators (3.2 g).

In conclusion, during one year of PA therapy, an SLE like syndrome develops in about 30% of patients. On the other hand, the ANA titer was not

even significantly raised in 25%. The syndrome is almost always reversible after discontinuation of PA therapy. The use of the drug is justified in patients at high risk for lethal arrhythmias until safer antiarrhythmic drugs become available. Subjective symptoms and a rapid pronounced rise in the ANA titer are the earliest signs. On the other hand, a phenotypic test seems to be of little value in predicting when the therapy is guided by plasma levels, resulting in the same PA plasma level in both slow and rapid acetylators.

## REFERENCES

- 1 Aarden L A, de Groot E S R & Felik W. Immunology of DNA III. Crithidia as a simple substrate for the detection of anti-DNA immunofluorescence technique. *Ann NY Acad Sci* 254: 505, 1975.
- 2 Alarcón Segovia D. Drug induced lupus. *Mayo Clin Proc* 44: 664, 1969.
- 3 Blomgren S E, Condemni J J, Bignall, Vaughan J H. Antinuclear antibody to procainamide. A prospective study. *N Engl J Med* 281: 64, 1969.
- 4 Blomgren S E, Condemni J J & Vaughan J H. Procainamide induced lupus erythematosus. *Med* 52: 338, 1972.
- 5 Campbell W, Tilstone W J, Lawson D, ton I & Lawrie T D V. Acetylator phenotype: the clinical pharmacology of slow-release procainamide. *Br J Clin Pharmacol* 3: 1023, 1971.
- 6 Coons A H & Kaplan M H. Local anesthetic in tissue cells. *J Exp Med* 91: 1, 1950.
- 7 Drayer D E & Reidenberg M M. Cosequences of polymorphic acetylation of procainamide. *Clin Pharmacol Ther* 22: 251, 1977.
- 8 Evans D A P. Genetic variations in the metabolism of isoniazid and other drugs. *Ann NY Acad Sci* 151: 723, 1968.
- 9 Evans D A P & White R T A. Human polymorphism. *J Lab Clin Med* 63: 394, 1964.
- 10 Frislid K, Berg M, Hansteen V & Lunde M. Comparison of the acetylation of procainamide and sulfadiazine in man. *Eur J Clin Pharmacol* 9: 433, 1976.
- 11 Graffner C, Jansson R M, Lagerström Persson B A. Disposition of procainamide acetylated metabolite after acute administration determined by a sensitive method based on chromatography. *Eur J Drug Metab Pharmacol* 1: 29, 1977.
- 12 Hännegren Å, Borgå O & Sjöqvist F. Isotonicity of isoniazid (INH) in Swedish tuberculosis before and during treatment with para-aminosalicylic acid (PAS). *Scand J Respir Dis* 51: 61, 1970.
- 13 Hansson K A & Sandberg M. Deterioration of sulphapyridine and its metabolites in

23. Enslin J. Effects of administration of salicylazosulphapyridine. *Acta Pharm Suec* 10: 87, 1973.
24. Rungsten N C, Cederberg Å, Hanson A & Karlsson B W. Effects of long term treatment with procainamide. *Acta Med Scand* 198: 475, 1975.
25. Karlsson E & Moln L. Polymorphic acetylation of procainamide in healthy subjects. *Acta Med Scand* 197: 99, 1975.
26. Karlsson E, Moln L, Norlander B & Sjoqvist F. Acetylation of procainamide in man studied with a gas chromatographic method. *Br J Clin Pharmacol* 1: 467, 1974.
27. Weser J & Klein S W. Procainamide dosages: schedules, plasma concentrations and clinical effects. *JAMA* 215: 1454, 1971.
28. Flier D, Carr R I, Agnello V, Fiezi T & Sikel H G. Antibodies to polynucleotides. Distribution in human sera. *Science* 166: 1648, 1969.
29. Jowski B D, Taylor J, Lown B & Ritchie R. Long term use of procainamide following acute myocardial infarction. *Circulation* 47: 1204, 1973.
30. Karlsson R, Karlsson E & Moln L. Spontaneous systemic lupus erythematosus and acetylator phenotype. *Acta Med Scand* 201: 223, 1977.
31. Pick A I, Avdor I & Ben Bassat M. A clinicopathological study of a patient with procainamide induced systemic lupus erythematosus. *Rheum Dis* 35: 181, 1976.
32. Land L, Campbell L K & Robertson B J. Enzymatic coupling of isoniazid to proteins. *Biochemistry* 11: 434, 1972.
33. Her J R, Whitney J M, Chambers J S & Jones D J. The quantitative determination of isoniazid and para-aminosalicylic acid in body fluids. *Rev Tuberc* 76: 85, 1957.
34. Moln L, Larsson R & Karlsson E. Evaluation of the sulphapyridine acetylator phenotype in healthy subjects and in patients with cardiovascular diseases. *Acta Med Scand* 201: 217, 1977.
35. Perry H M. Late toxicity to hydralazine resembling systemic lupus erythematosus or rheumatoid arthritis. *Am J Med* 54: 58, 1973.
36. Reidenberg M M, Drayer D E, Levey M & Warner H. Polymorphic acetylation of procainamide in man. *Clin Pharmacol Ther* 17: 72, 1975.
37. Reidenberg M M, Drayer D, De Marco A L & Bellow C T. Hydralazine elimination in man. *Clin Pharmacol Ther* 14: 970, 1973.
38. Reidenberg M M & Martin J H. Acetylator phenotype of patients with systemic lupus erythematosus. *Drug Metab Dispos* 7: 71, 1974.
39. Schroder H & Evans D A P. The polymorphic acetylation of sulphapyridine in man. *Med Genet* 9: 168, 1972.
40. Strandberg I, Boman G, Hassler F & Sjoqvist F. Acetylator phenotype in patient with hydralazine induced lupoid syndrome. *Acta Med Scand* 200: 367, 1976.
41. Whittle T S & Answorth S K. Procainamide induced systemic lupus erythematosus. Renal involvement with deposition of immune complexes. *Arch Pathol Lab Med* 100: 469, 1976.
42. Woosley R L, Drayer D E, Reidenberg M M, Nes A S, Carr K & Oates J A. Effect of acetylator phenotype on the rate at which procainamide induces antinuclear antibodies and the lupus syndrome. *N Engl J Med* 298: 1157, 1978.





# Effect of Physical Training on Different Categories of Patients with Intermittent Claudication

Tommy Jonason Berit Jonzon Ivar Ringqvist and Aina Oman Rydberg

From the Department of Clinical Physiology, Västerås Central Hospital, Västerås, Sweden

**ABSTRACT** The effect of supervised training was studied in 69 patients with intermittent claudication. Initial walking distance was measured on a treadmill. Eight of the patients had resting pain in the leg when recumbent (group A), 25 had an initial walking distance of less than 500 m (group B), 11 had an initial walking distance of 500-1 000 m (group C), and 25 had coronary insufficiency (group D). The study showed that training should be undertaken for at least 3 months. In some patients with resting pain, training led to relief of pain and surgical treatment was necessary. Almost all patients without signs of coronary insufficiency increased their walking distance compared to only 14 of the 24 patients with coronary insufficiency. Walking distance increased significantly in groups B and C and no significant difference was found between patients with proximal and distal arterial stenosis.

garded as an absolute indication for reconstructive surgery (6). It is well known that a high percentage of patients with intermittent claudication have coronary insufficiency (9). We have not seen any study on the effect of physical training in this group of patients.

Some studies have shown that the more proximal the arterial stenosis, the less the effect of training (18). This finding does not accord with our experience. Therefore we have undertaken a study to find out: first, if training has any effect on patients with resting pain; second, if there is a difference in the effect of training between patients with and without coronary insufficiency; and third, if there is a difference between patients with proximal or distal arterial stenosis.

## METHODS AND PATIENTS

### Examination

Each patient was examined by measuring the BP in the thigh, calf, ankle and toe with occlusion-cuffs and strain gauges. Also, the pulses in the femoral and popliteal arteries were evaluated with the Doppler shift technique. The BPs in the legs were assessed relative to the pressure in the right arm, but the pressure in the left arm was used if it was at least 10 mmHg higher than in the right arm. The patients were tested before the start of training and after 1½ and 3 months of training. Some patients continued training for a further 3 months and were then tested again. The tests included measurement of maximal walking distance on a treadmill with a subjective evaluation of leg pain. The patients started with a load of 30 W, which was then increased by 30 W every 6th minute. The speed of the treadmill was 1 m/s. The patients walked until either the pain in the leg was no longer bearable, angina pectoris occurred or general fatigue or dyspnea intervened. The test was also interrupted if the systolic BP exceeded 270 mmHg. ECG was recorded continuously during the test.

The leg pain was rated according to a 15 grade scale modified from Borg (2) as follows: 1-2 (none)—3-4 (very light)—5-6 (fairly light)—7-8 (somewhat severe)—9-10 (severe)—11-12 (very severe)—13-14 (very very severe)—15. To assess the effect of training on leg pain, we

*Address:* intermittent claudication, physical therapy  
Acta Med Scand 206 253 1979

Other studies have shown the beneficial effect of physical training in patients with intermittent claudication (4, 12, 14, 22). Improved peripheral circulation of oxygen (22), improved glycolytic and oxidative metabolic capacity (8) and improved walking technique (19) have been suggested as reasons for the improvement with training. An increase in the collateral inflow capacity after training has been demonstrated in animal experiments (16) and in clinical studies (5). Skinner and Strandness (20) also found an increased blood pressure (BP) at rest after training, and also a less reduction in ankle pressure after work. These changes were considered to result from an increased collateral circulation. However, Dahlöf found no changes in BP at rest in the calf after training. Some authors have considered reconstructive surgery to be the treatment of choice for resting pain (17) and resting pain has been re-

Table 1 Patients with intermittent claudication who completed supervised training in 1974/75

	N	Average age (y)	BP relative to that in the arm (mmHg)		Duration of intermittent claudication (mo)	
			Thigh	Toe	Median	Range
Group A	8	65	-24	-95	12	3-170
Group B	25	65	-35	-101	24	2-144
Group C	11	62	-29	-87	18	6-84
Group D	24	65	-32	-101	24	2-146

compared the rating of leg pain after the same distance in each of the three tests (pretraining, after 1 and 3 months). The distance chosen for each patient was the individual pretraining maximum walking distance.

### Patients

Seventy eight patients with a walking distance less than 1000 m on the treadmill but without gangrene started supervised training between March 1974 and Dec 1976. Two patients discontinued training because of coxarthrosis and knee joint disease, respectively. Three patients were admitted to hospital during the training period because of myocardial infarction, cerebral vascular disease and gastrointestinal disease, respectively. Two patients had to stop because of cardiomegaly and uncontrolled atrial fibrillation, respectively. Two patients stopped training of their own accord. One patient was admitted to vascular surgery after 1 month of training. The remaining 68 patients (age range 49-86 years) of whom 49 (70%) were men, had had intermittent claudication for 2-156 months (Table 1).

The patients were divided into four groups. Group A: 8 patients with resting pain in the leg when recumbent. None of them had diabetes mellitus. All had been awakened on several occasions by pain in the leg relieved when lowering the leg. This pain was easily differentiated from cramp and the restless legs syndrome, the latter experienced by 14 of the other patients. Group B: 25 patients who had an initial walking distance of less than 1000 m. Group C: 11 patients who had an initial walking distance of 500-1000 m. Group D: 24 patients with signs of insufficiency in the exercise ECG and/or a history of angina pectoris. There were no differences in age or segmental BPs between these four groups (Table 1). Thirteen of the 36 patients in groups B and C had proximal arterial stenosis, which was defined as a BP in the thigh at least 25 mmHg lower than in the arm (13) and loss of the diastolic component in the pulsations in the femoral artery evaluated with the Doppler shift technique (21).

### Training

The patients trained in groups in the Department of Clinical Physiology for 30 min twice a week for three months under the guidance of a physiotherapist. Eight of the patients with coronary insufficiency continued their training for another 2-3 months. Before starting the training we informed the patients about the disease and the available

means of treatment. Also we went through a programme for training at home and emphasized the importance of daily walks in addition to the formal programme.

The aim of the training was to increase the walking distance by improving peripheral circulation, endurance and strength, patient fitness, good walking technique, co-ordination and balance. Training consisted of simple movements of feet and legs at almost maximal pain occurred. The most effective training is achieved in the standing position, e.g. limbering up, jumping, dancing and rope skimming. Each training session most of the patients also exercised on bicycles. The training was adapted to the condition of the patient. For example, those with coronary insufficiency started by warming up sitting and continued alternately standing and sitting. To get the peripheral effect of training in these patients, we also induced angina pectoris, the exercises were also performed with each leg separately.

### Statistics

Student's *t* test for paired and unpaired observations was used for statistical calculations.

## RESULTS

### Group A—resting pain

After three months of training, six of the eight patients in this group no longer had resting pain. Of these six, four had had resting pain 1-3 times per week for two weeks to one year and a history of claudication for less than two years. The sixth patient had resting pain up to three times per night for two weeks and claudication for only three months. The two patients who did not improve had more frequent attacks of resting pain (3 times per night) for at least two months. One had had claudication for three years, the other for ten years.

The six patients who improved more than doubled their walking distance after three months of training ( $p < 0.01$ ), while the other two reached a slight increase in their walking distance.

# Changes in walking distance and leg pain in patient groups B, C and D

	Pre training	Posttraining (mo)	
		1½	3
n=5)			
walking distance (m)	261	477	583
walking distance (m)		+211 *	+322 *
(degree)			
maximal walking distance	12.7	10.5 *	11.3
maximal pretraining walking distance			
61 m)	12.7	8.7***	6.4 *
n=11)			
walking distance (m)	697	740	897
walking distance (m)		+43	+198 *
(degree)			
maximal walking distance	12.0	10.6	10.9
maximal pretraining walking distance			
97 m)	12.0	10.1	10.7
n=24)			
walking distance (m)	470	598	597
walking distance (m)		+128	1
maximal walking distance (degree)	12.0	10.5	9.5**
p<0.01	p<0.001		

Patients who improved had an average ankle of 65 mmHg (range 45-100) the other two of 55 mmHg respectively. One of these later underwent reconstructive vascular

walking distance less than 500 m

as a significant increase in walking distance months of training ( $p<0.001$ ) and a further after three months ( $p<0.01$ ) when the walking distance was more than doubled. The patients rating of the leg pain at the premaximal walking distance was significant at the 1½ month (8.7) and 3 month tests and at the pretraining test (12.7) ( $p<0.001$ ). All patients except two had increased the walking distance at the three month test. One of the two improvement continued training for another months and achieved a clear increase at a test performed thereafter.

walking distance 500-1000 m

walking distance did not increase significantly after three months of training ( $p<0.01$ ). Also subjective assessment of leg pain at the max

imum pretraining walking distance showed no improvement at either the 1½ month (10.1) or 3 month test (10.7) compared with the pretraining test (12.0).

Eight of the 11 patients increased the walking distance after three months of training. One of the three patients who did not improve had coxarthrosis and one increased his walking distance at a test performed after a further three months.

## Group D—coronary insufficiency (Tables II and III)

The patients in this group increased the walking distance significantly after 1½ months of training ( $p<0.01$ ) but there was no further significant increase after that. After the full three months of training 14 patients increased the walking distance while 10 did not. There were no differences in the duration of claudication or in segmental BPs between those who improved and those who did not. In the patients who improved the subjective rating of leg pain at the maximal pretraining walking distance (mean 450 m) was significantly lower after three months of training (7.8) than at the pretraining test (11.9). Those who did not improve showed no significant difference in the ratings (11.1) compared to 12.2). At the three month test there were no significant differences in the leg pain ratings incl

Table III Patients with ECG changes indicating coronary insufficiency during the pretraining test and/or a history of angina pectoris (group D,  $n=24$ )

	Before training	After 3 months training
<i>Patients who improved (<math>n=14</math>)</i>		
Maximal walking distance (m)	450	736
Leg pain		
At maximal pretraining walking distance (mean 450 m)	11/9	7/8
At maximal walking distance	11/9	9/6
<i>Patients who did not improve (<math>n=10</math>)</i>		
Maximal walking distance (m)	500	406
Leg pain (degree) at maximal walking distance (mean 406 m)	12/2	11/1

\* $p<0.05$      $p<0.01$

dence of angina pectoris, heart rate or frequency of respiration at the end of the maximal walking test between those who improved and those who did not. Two of the patients who did not improve and three of those who did were on treatment with  $\beta$  receptor blocking drugs.

Three of the patients who did not increase their walking distance after three months of training continued training for another three months. After this extra period one showed an appreciable and two a moderate increase in their walking distances.

Table IV Patients with proximal and distal arterial stenosis in groups B and C ( $n=36$ )

	Before training	After 3 months training
<i>Proximal arterial stenosis (<math>n=13</math>)</i>		
Maximal walking distance (m)	347	687
Increase in walking distance (m)		+340 *
Leg pain (degree) at maximal pretraining walking distance (mean 347 m)	12/5	6/4 *
<i>Distal arterial stenosis (<math>n=23</math>)</i>		
Maximal walking distance (m)	440	686
Increase in walking distance (m)		+226***
Leg pain (degree) at maximal pretraining walking distance (mean 440 m)	12/6	8/7*

\*\*\* $p<0.001$

#### Proximal vs. distal arterial stenosis (Table IV)

Of the 36 patients in groups B and C with proximal arterial stenosis they had a significant increase in BP in the thigh, the average difference thigh and arm being  $-54$  mmHg against  $-11$  mmHg in the patients with distal arterial stenosis. There were no significant differences in ankle pressure.

Walking distances increased significantly after three months of training in those with proximal as well as in those with distal arterial stenosis ( $p<0.001$ ) and we found no difference in the effect of training. All but one patient among the proximal arterial stenosis increased their walking distance.

## DISCUSSION

### Length of the training period

Earlier studies have shown that patients with intermittent claudication increased their walking distance after 3–4 months of training (4, 10). Our study likewise showed an increase in walking distance after three months of training in all the patients with no signs of coronary artery disease. In fact, in group B there was already a significant increase in walking distance after 11 months of training. Some patients, however, needed more than three months of training. Our results support the idea of allowing patients with intermittent claudication to train for at least three months before any decision is made concerning vascular surgery.

### Resting pain

Resting pain has been considered to be a contraindication for vascular surgery (6) while others have attempted to treat it with prostaglandin synthase inhibitors (3). In previous articles treatment of intermittent claudication with hypertension and lumbar sympathectomy has been discussed. We found that patients with intermittent claudication and resting pain (1–3 times per week) for a relatively short time (less than a year) and not more than 10 years of claudication obtained a good result after three months of training with elimination of the pain and a more than doubled walking distance. The patients did not have the restless legs syndrome or other thrombotic conditions and there were no other non-ischemic causes of pain. The resting pain of low frequency does not seem to indicate a trial of training for three months.

# *Insufficiency*

patients with claudication have signs and/or symptoms of coronary insufficiency. Among our 35<sup>th</sup> had coronary insufficiency which is as frequently as others have found (9). In the three other patients had had a myocardial

74 patients with coronary insufficiency. 14 of the walking distance after three months while 10 did not. Among the 10 patients not improve two had angina pectoris at the age test. At the test after three months of another three patients had angina pectoris could explain the lack of an effect of training. With our non-invasive methods we did not observe difference between the two groups could explain the lack of an effect of training in the 7 patients. In an analysis of a large claudication patients who had undergone training it was found that overweight, age and coronary heart disease only influenced the change in walking distance. Impaired function of the left ventricle is one explanatory variable. Hellerstein (7) in a group of patients with angina pectoris without myocardial infarction that failing to train indicated not only more severe of artery disease but also more severe dilation of the left ventricle than response to

of the patients with no improvement continuing for another three months and had an increased walking distance at a test following this period of training. Thus it is possible that with coronary insufficiency need a longer of training. During the walking tests these walked with a load on the treadmill and it is that the result would have been different if walked on the flat.

# *Is distal arterial stenosis*

with proximal stenosis have a higher concentration of lactate in blood from the femoral vein than patients with distal stenosis (14). Because of arterial insufficiency in large muscle groups. It has been shown that the proximal the stenosis the less the effect of (18). We did not find any significant difference the effect of training between patients with and those with distal arterial stenosis

both showing a significant increase in walking distance after three months of training. However none of the patients with proximal stenosis had low BP in the thigh. The average thigh pressure 101 mmHg (range 70-185) and the average difference between thigh and arm pressure 5 mmHg (range -25 to 100). One would not expect patients with a greater difference between thigh and arm pressure to show such a good result from training.

## REFERENCES

- 1 Alpert J, Larsen A & Lassen N. Blood flow in the calf muscle during walking studied by the Xenon 133 clearance method. *Circulation* 39: 353, 1967.
- 2 Borg G. Simple rating methods for estimating perceived exertion. In: *Physical work and effort*, p. 39. Pergamon Press, Oxford, 1977.
- 3 Carlsson L, Jogestrand T, Kajer L & Lilja A. Kliniska erfarenheter med prostaglandin i vid perifer artersjukdom. *Lakartidningen* 4: 69, 1971.
- 4 Dahllof A-G. Perifer arteriell insufficiens i nedre extremiteterna. Thesis. Gothenburg 1975.
- 5 Ericsson B, Haeger K & Lindell S-E. Effect of physical training on intermittent claudication. *Angiology* 21: 188, 1970.
- 6 Hallbook T & Hegedus V. Angiograf vid perifer artersjukdom i nedre extremiteterna. *Lakartidningen* 70: 371, 1973.
- 7 Hellerstein H-K. Anatomical factors influencing effects of exercise therapy of ASHD subjects. In: *Das chronische kranke Herz* (ed. H. Rosskam & H. Reindell), p. 513. Schattauer, Stuttgart, 1973.
- 8 Holm J. Skeletal muscle metabolism in patients with peripheral arterial insufficiency. Thesis. Gothenburg 1972.
- 9 Hughson W-G, Mann J-I & Garrod A. Intermittent claudication: prevalence and risk factors. *Br Med J* 1: 1379, 1978.
- 10 Krause D & Dittmar K. Ergebnisse bei der physikalischen Therapie peripherer arterieller Durchblutungsstörungen (III). *Munch Med Wochenschr* 116: 385, 1974.
- 11 Krause D, Stang A & v. Zezschwitz W. Bedeutung prognostischer Faktoren für die Ergebnisse krankengymnastischer Übungsbehandlung bei Claudication. *Munch Med Wochenschr* 119: 1289, 1977.
- 12 Larsen A & Lassen N. Effect of daily muscular exercise in patients with claudication. *Intermittens*. *Lancet* 2: 1093, 1966.
- 13 Nelsen P-E, Bell G & Lassen N. Strain gauge studies of distal blood pressure in normal subjects and in patients with peripheral arterial disease. *Scand J Clin Lab Invest (Suppl)* 178: 103, 1973.
- 14 Pernow B & Zetterquist S. Metabolic evaluation of the leg blood flow in claudicating patients with arterial obstruction at different levels. *Scand J Clin Lab Invest* 21: 277, 1968.

- 15 Porje I G & Lundberg A Preliminara erfarenheter av systematisk muskeltraning vid claudicatio intermittens *Opusc Med* 8 211 1957
- 16 Sanne H & Sivertsson R The effect of exercise and the development of collateral circulation after experimental occlusion of the femoral artery in the cat *Acta Physiol Scand* 73 257 1968
- 17 Scherstén T Fysisk trining vid perifer arteriell in sufficiens *Lakartidningen* 74 3897 1977
- 18 Schmidtke I Bisherige Ergebnisse eines mehr wöchigen Trainings *Akt Probl Angiol* 18 75 1973
- 19 Schoop W Mechanism of beneficial action of daily walking training of patients with intermittent claudication *Scand J Clin Lab Invest (Suppl 128)* 8
- 20 Skinner J & Strandness E Exercise and intermittent claudication II Effect of physical Circulation 36 23 1967
- 21 Yao S T Hobbs J T & Irvine W J examination by an ultrasonic method *Br J Med* 4 555 1968
- 22 Zetterquist S Effect of daily training on the blood flow in exercising ischemic legs *Scand J Clin Lab Invest* 25 101 1970

## Prognostic Significance of Lymphopenia in Sarcoidosis

Olof Selroos and Elli Koivunen

*From the Fourth Department of Medicine, Helsinki University  
Central Hospital, Helsinki, Finland*

ACT. During 1959-67, sarcoidosis was diagnosed in a series of 140 patients. All were followed. 22 developed chronic sarcoidosis. In 134 (20 with chronic course) the initial granulocyte and lymphocyte counts were known. Differences in granulocyte values were seen between different groups of sarcoidosis patients. Patients with erythema nodosum had significantly higher monocyte levels. Lymphopenia below 1000/seen in only 7.5% of the patients. Lymphocytes below 1500/ $\mu$ l were a common finding. In patients developing chronic sarcoidosis, initially decreased lymphocyte values were also seen in patients older than 40 years at the time of diagnosis, in patients negative to 10 TU of PPD and in patients with a disease requiring treatment with corticosteroids. A correlation was found between lymphopenia and less favourable prognosis. In the patients having a very good prognosis, the initial lymphopenia must be carefully studied up. The initial presence of erythema nodosum does not always guarantee a good prognosis.

*Key words:* sarcoidosis, lymphopenia, prognosis.  
*Acta Med Scand* 206: 259, 1979.

The prognosis of sarcoidosis varies. It used to be considered poor because only the lesions typical of chronic disease were recognized. Today we know that the prognosis is usually good. However, some patients develop a chronic disease which may be characterized by pulmonary fibrosis with respiratory insufficiency, hypercalcaemia with renal insufficiency, hypercalcaemia and bone cysts. These patients benefit from long-term treatment with corticosteroids and have subjective symptoms (1). Indications for corticosteroid therapy in sarcoidosis are usually clear. Patients with non-fibrotic lesions may disappear spontaneously but some remain stable or deteriorate. Prospective

controlled studies have indicated that it is unnecessary to treat every patient (18). However, there is no clinical sign which indicates that a patient will definitely develop a chronic disease, have a poor prognosis and perhaps continuously require corticosteroids.

During the years 1959-67 a series of sarcoidosis patients was examined clinically (15). They have been followed up for more than 10 years. We have now analysed the initial granulocyte, monocyte and lymphocyte counts in the patients who subsequently developed a chronic disease and compared these data with corresponding values for other groups of sarcoidosis patients and healthy controls.

## PATIENTS AND METHODS

The investigation was carried out on 140 sarcoidosis patients diagnosed in 1959-67. The clinical picture and diagnostic criteria have been reported elsewhere (15). Differential leukocyte count was made initially in 134 of the patients. None of the patients was receiving corticosteroids for other diseases at the time of the diagnosis of sarcoidosis. Of the 6 patients whose initial differential count was unknown, 2 developed a chronic disease.

The follow-up examination disclosed that 22 patients (15.7%) developed chronic sarcoidosis with pulmonary fibrosis and moderate to severe functional impairment. Four patients with a chronic disease have died: three of uraemia and one of respiratory failure. Continuous activity of the disease has been a typical sign of the chronic condition, presenting as a fluctuating chest X-ray finding, variation in lymph node size, development of splenomegaly and bone cysts, and often as new skin lesions.

Of the 22 patients with chronic sarcoidosis, 14 (64%) were females. In the non-chronic group, 69% were females (Table I). Some other clinical signs are also listed in Table I. The age at diagnosis was significantly higher in the patients developing chronic disease than in those with a limited non-chronic disorder. Of the chronic patients, 68% were initially negative to 10 TU of PPD against only 41% in the non-chronic group. This difference is also significant. The presence of erythema nodosum, positive skin reaction to 1 TU hypercalcaemia or hypercalcaemia



Table I Initial data on 140 sarcoidosis patients diagnosed during 1959-67 and grouped according to results of follow up examinations more than 10 years later

	Patients who developed chronic sarcoidosis (Age at diagnosis $45.5 \pm 11.0$ )		Patients whose sarcoidosis was cured (Age at diagnosis $38.7 \pm 10.7$ )	
	N	%	N	%
Total	22	15.7	118	84.3
Females	14	64	81	69
Erythema nodosum	2	9	27	23
1 TU +	2	9	30	25
10 TU +	5	23	40	34
10 TU -	15	68	48	41
Chest X ray				
Stage I	8	36	69	58
Stage II	14	64	49	42
Hypercalcaemia	6/21	29	16/110	15
Hypercalciuria	6/17	35	15/89	17

Statistically significant differences exist between chronic and non-chronic patients with respect to age at diagnosis ( $p < 0.01$ ) and 10 TU negative skin reactions ( $\chi^2 = 5.67$   $p < 0.025$ ).

did not influence the prognosis. Neither was the initial chest X-ray finding a prognostic sign.

The total number of leukocytes and the numbers of granulocytes, monocytes and lymphocytes at the time of diagnosis were calculated in 134 sarcoidosis patients and in 40 healthy controls of the same age and sex.

## RESULTS

The numbers of leukocytes, granulocytes, monocytes and lymphocytes are shown in Table II.

The leukocyte count was normal in all groups of sarcoidosis patients. No significant differences

were noted in granulocyte counts between sarcoidosis patients and healthy controls or between different groups of sarcoidosis patients.

The monocytes were normal in all groups of sarcoidosis patients except for those with erythema nodosum who had a significantly increased count compared with the healthy controls ( $p < 0.01$ ).

The greatest variations were noted in lymphocyte counts. The lowest values were among the patients who developed chronic sarcoidosis. Their mean lymphocyte value was significantly lower than that of the controls.

### II Leukocyte, granulocyte, monocyte and lymphocyte counts/ $\mu$ l (mean $\pm$ S.D.) at the time of diagnosis in different groups of sarcoidosis patients and healthy controls

	N	Leukocytes	Granulocytes	Monocytes	Lymphocytes
Healthy controls	40	$6,600 \pm 1,500$	$4,146 \pm 1,360$	$348 \pm 215$	701
Female patients	91	$6,500 \pm 1,600$	$4,066 \pm 1,301$	$395 \pm 248$	1879
Male patients	43	$6,800 \pm 2,000$	$4,171 \pm 1,504$	$457 \pm 349$	1946
Patients below 40 y	69	$6,800 \pm 1,800$	$4,233 \pm 1,369$	$409 \pm 250$	1941
Patients above 40 y	65	$6,300 \pm 1,800$	$3,947 \pm 1,347$	$417 \pm 313$	1464
Erythema nodosum	29	$7,600 \pm 1,500$	$4,976 \pm 1,472$	$510 \pm 278$	1991
1 TU +	32	$6,900 \pm 2,000$	$4,199 \pm 1,586$	$427 \pm 226$	2077
Chest X-ray					
Stage I	71	$6,900 \pm 1,800$	$4,376 \pm 1,326$	$386 \pm 250$	1900
Stage II	63	$6,200 \pm 1,700$	$3,772 \pm 1,347$	$449 \pm 315$	1749
Patients not immediately treated	79	$6,900 \pm 1,700$	$4,312 \pm 1,362$	$371 \pm 222$	2058
Patients immediately treated	55	$6,100 \pm 1,800$	$3,780 \pm 1,308$	$474 \pm 343$	1590
Patients developing chronic sarcoidosis	20	$6,000 \pm 1,900$	$3,834 \pm 1,345$	$465 \pm 334$	1486
Patients developing non-chronic disease	114	$6,700 \pm 1,700$	$4,180 \pm 1,342$	$406 \pm 272$	1913

$p < 0.001$ ) and of the sarcoidosis patients not having a chronic disease ( $p < 0.01$ ). Out of 20 patients 12 had an initial lymphopenia (lymphocyte count  $< 1500/\mu\text{l}$ ) the lowest value being  $500/\mu\text{l}$ . A lymphocyte count below  $1500/\mu\text{l}$  was in only 27 patients out of 118 (23%) in the group. However the disease was spontaneously in only 4 of these 27 patients. Other 23 required treatment with corticosteroids and the signs of disease activity did not clear during the first two years. Lymphocyte below  $1000/\mu\text{l}$  were seen in only 10 patients. Mean lymphocyte values of female and male sarcoidosis patients did not differ significantly from other or from the values of the controls. There was no difference in lymphocyte values between patients above and below 40 years at the time of diagnosis. However those over 40 years had a slightly lower mean lymphocyte value than the controls ( $p < 0.05$ ). Sarcoidosis patients with stage II pulmonary infiltrations had initially a lower mean lymphocyte value than the patients with stage I finding but the difference was not statistically significant. Patients whose sarcoidosis was considered so severe and/or spread or active that therapy with corticosteroids was started immediately had a significantly lower mean lymphocyte value than the controls ( $p < 0.001$ ) and the patients not requiring steroids ( $p < 0.001$ ). The later had the highest mean lymphocyte value ( $2038/\mu\text{l}$ ) together with those with a positive skin reaction to 1 TU of PPD ( $2072/\mu\text{l}$ ).

## DISCUSSION

Reviews state that leukopenia is not an unusual finding in sarcoidosis (1-13). The leukopenia was found to be due to a reduction of lymphocytes. Anderson (10) noted that 33% of sarcoidosis patients had lymphocyte counts below  $1000/\mu\text{l}$  and that an lymphocyte value was significantly lower than that of healthy controls. He also found that leukopenia was more common in patients with radiographic evidence of lung involvement. In patients with chronic persistent disease and in those with subacute transient disease Anderson (2) found the same frequency of initial lymphopenia among 140 patients with pulmonary stage sarcoidosis. The occurrence of lymphopenia in sarcoidosis has been repeatedly verified and shown to be due to

a reduction in thymus-dependent lymphocytes—T cells (5, 6, 9, 12, 14, 19, 20) and the present study. The number of B-cells is either normal (1, 4, 9) or reduced (20) or slightly elevated (6, 7, 14). Estimates of lymphocyte subpopulations could not be obtained at the time of diagnosis in our patients.

Böttger (3) has drawn attention to rising lymphocyte values in patients with spontaneously regressing disease. Patients on corticosteroid therapy have lower lymphocyte values than non-treated sarcoidosis patients (14). In patients treated with corticosteroids the relapse rate after treatment has been found to be significantly higher among those with persistent lymphopenia (4).

In Finland the prognosis of sarcoidosis is usually good (15-17) and particularly favourable when associated with female sex, young age, erythema nodosum and positive skin tests with 0.1-1 TU of PPD (8). The prognosis was not influenced by differences in sex, presence of erythema nodosum or initial chest X-ray findings in our series. Patients negative to 10 TU of PPD had a poorer prognosis than those positive to 10 TU. The lymphocyte values were as a rule significantly lower in patients with a poor prognosis.

A correlation exists between the prognosis of sarcoidosis and delayed type hypersensitivity reactions. In Finland sarcoidosis patients as a group have depressed skin reactivity to PPD but individual patients may not show any reduction (15). Most patients with a depressed reactivity to PPD at the time of diagnosis regain their normal skin sensitivity to PPD when sarcoidosis is cured—spontaneously or after treatment with corticosteroids (16). Patients with a less favourable prognosis usually remain tuberculin negative. The delayed type hypersensitivity reactions are controlled by the T-cells. It is therefore understandable that a reduction in lymphocytes caused by a depletion of T-cells is correlated with the prognosis of the disease (21).

This investigation clearly indicates the relationship between lymphopenia and the prognosis of sarcoidosis. The initial lymphopenia in this population (lymphocytes  $< 1500/\mu\text{l}$ ) seems to be of greater prognostic significance than previously believed. Initial lymphopenia was a common finding among the patients who developed a chronic disease but very rare among those who had a disease with good prognosis. This obvious difference may be partly influenced by the composition of the series in our country where initial lymphopenia below  $1000/\mu\text{l}$

is a rare finding in sarcoidosis patients. Lymphopenia of this degree was seen in only 10 (7.5%) of our patients compared to one third of patients in other series (2-10).

Although a small proportion of the sarcoidosis patients with initial lymphopenia have a good prognosis, the finding of lymphocyte reduction usually heralds a long standing and chronic disease with a poor prognosis. The finding of initial lymphopenia indicates a very careful follow up. On the other hand, those with initially normal or high lymphocyte counts and usually—as a consequence of this—positive skin reactions to at least 10 TU of PPD have a good prognosis and can be followed up without therapy.

# REFERENCES

- 1 Bruschi M & Howe J S. Classification of the hematologic variations and abnormalities associated with Boeck's sarcoid: review of the literature. *Blood* 5: 478, 1950.
- 2 Böttger D. Die initiale absolute Lymphopenie bei der Lungensarkoidose. *Z. Erkr. Atmungsorgane* 130: 209, 1969.
- 3 — The blood picture in pulmonary sarcoidosis—prognostic aspects. In: Fifth International Conference on Sarcoidosis (ed. L. Levinsky & F. Machold), p. 535. Universita Karlova, Praha, 1971.
- 4 — Zur prognostischen Bedeutung der absoluten Lymphopenie unter der Prednisolontherapie der chronischen Lungensarkoidose. *Z. Erkr. Atmungsorgane* 144: 39, 1976.
- 5 Cumiskey J M, McLaughlin H & Keelan P T. T and B lymphocytes in sarcoidosis: a clinical correlation. *Thorax* 31: 665, 1976.
- 6 Daniele R P & Rowlands D T Jr. Lymphocyte subpopulations in sarcoidosis: correlation with disease activity and duration. *Ann Intern Med* 85: 593, 1976.
- 7 Fernandez B, Press P & Girard J P. Distribution and function of T and B cell subpopulations in sarcoidosis. *Ann NY Acad Sci* 278: 80, 1976.
- 8 Hannuksela M, Salo O P & Mustakallio K K.

- The prognosis of acute untreated sarcoidosis. *Clin Res* 2: 57, 1970.
- 9 Hedfors E. Immunological aspects of sarcoidosis. *Scand J Respir Dis* 46: 1, 1975.
  - 10 Hoffbrand B I. Occurrence and significance of lymphopenia in sarcoidosis. *Am Rev Respir Dis* 103: 1968.
  - 11 Johns C J, Macgregor M I, Zachary W C. Extended experience in the long-term steroid treatment of pulmonary sarcoidosis. *Acad Sci* 278: 722, 1976.
  - 12 Karana Y P, LoBuglio A F, Bromberg H, Hurlbut H E. Sarcoid lymphocytes: quantitation. *Ann NY Acad Sci* 278: 69, 1976.
  - 13 Mayock R L, Bertrand P, Morris S, Scott J H. Manifestations of sarcoidosis of 145 patients with a review of nine years from the literature. *Am J Med* 35: 67, 1976.
  - 14 Ramachandrar K, Douglas S D, Siltz R N. Peripheral blood lymphocyte counts in sarcoidosis. *Cell Immunol* 16: 6, 1976.
  - 15 Selroos O. The frequency, clinical picture and prognosis of pulmonary sarcoidosis in Finland. *Scand (Suppl)* 503, 1969.
  - 16 Selroos O & Niemistö M. Tuberculin active and cured sarcoidosis in Finland. In: Proceedings of the VI International Conference on Sarcoidosis (ed. K. Iwai & Y. Hosoda), p. 475. Tokyo Press, Tokyo, 1974.
  - 17 Selroos O, Niemistö M & Riska A. A study of treated and untreated early pulmonary sarcoidosis. In: Proceedings of the VI International Conference on Sarcoidosis (ed. K. Iwai & Y. Hosoda), p. 525. University of Tokyo Press, Tokyo, 1974.
  - 18 Selroos O & Sällgren T L. C. Therapy of pulmonary sarcoidosis: A evaluation of alternate day and daily dose. *Scand J Respir Dis*. In press.
  - 19 Sørensen S F, Hardt F & Veien A. Variation of lymphocyte subpopulations in the blood of patients with sarcoidosis. *Scand J Clin Lab Invest* 37: 1117, 1976.
  - 20 Tannenbaum H, Rocklin R E, Scheffer A L. Immune function in sarcoidosis. Studies on delayed hypersensitivity, B cells, serum immunoglobulins and serum components. *Clin Exp Immunol* 6: 1, 1976.
  - 21 Topilsky M, Shohat B, Spitzer S & Rabinovitch H. Relationship between T rosette formation and humoral immunity in sarcoidosis. *Ann NY Acad Sci* 278: 109, 1976.

# Glibenclamide and Glipizide in Maturity Onset Diabetes

## A Double Blind Cross over Study

G Blohme and J Waldenström

From the Departments of Internal Medicine II and Clinical Chemistry, Sahlgrenska Hospital, University of Göteborg, Göteborg, Sweden

The effects of glibenclamide and the concentrations of S-glucose, S-insulin and on the 24-hour urinary glucose excretion were studied in 37 patients with maturity onset diabetes. A double blind cross-over, double-blind technique was used. The fasting S-insulin concentration was higher during glibenclamide while the increase in insulin concentration postprandially was stronger during glipizide, supporting the concept that glipizide has a more prolonged and glipizide a stronger effect on insulin secretion. The S-insulin concentration was lower in the fasting state as well as hour postprandially during glibenclamide and together with a lower 24-hour urinary glucose excretion indicates that glibenclamide has a stronger blood glucose lowering effect. Although not significant, the differences were marginal in the clinical point of view. The lipid levels remained unchanged.

maturity onset diabetes, double blind cross-over, glibenclamide, glipizide, sulphonylureas, hypoglycaemic, oral antidiabetic substances.  
Scand J Clin Lab Invest 1979; 40: 263-267

If treating maturity onset diabetes is not only to relieve symptoms but also to prevent late complications including cardiovascular disease, it is generally accepted that normalization of blood glucose homeostasis is essential to these aims. A diet restricted in fat and carbohydrates and thus in energy is in combination with exercise the mainstay of diabetes treatment leading to desirable weight reduction in the always overweight maturity onset diabetic. Diet and exercise are not capable of normalizing the blood glucose level, a sulphonylurea (SU) derivative is nowadays the drug of choice, as biguanides carry a risk of lactic acidosis.

In the so-called second generation group of the SU, glibenclamide and glipizide—both with well documented potent antidiabetic properties (10, 11) and low toxicity (14, 17, 23)—exhibit interesting pharmacokinetic and pharmacodynamic differences (1, 5, 12, 19) which may affect the clinical effect with respect to the possibility of maintaining a normal blood glucose level both in the present and in the future, i.e. prevention of possible secondary failure.

When comparing short term effects of drugs in a clinical trial, several factors irrespective of the drug itself may influence the results. This is especially true with respect to the blood glucose lowering effect of antidiabetic drugs as the results are extremely dependent on the patients' adherence to their diet and their exercise. The psychological effect of changing the drug will consciously or unconsciously lead to a tightening up of the diet. One can never be sure when changing SU drugs whether the better balance in the blood glucose homeostasis depends on the change itself or which is more probable, changes in other factors.

In an attempt to eliminate these very important auxiliary factors, the present comparative short term study between glibenclamide and glipizide was undertaken with a double blind cross-over technique. Diabetics with hyperglycaemia despite 15 mg of one or the other of the drugs daily were selected in order to elucidate the difference in serum glucose and serum insulin levels, as well as in the excretion of glucose in urine per 24 hours.

## STUDY POPULATION AND METHODS

Forty patients with maturity onset diabetes—20 on glibenclamide and 20 on glipizide—were chosen according to the following criteria: 1) Fasting S-glucose  $>7.2$  mmol/l with or without glucosuria despite 15 mg of glibenclamide or glipizide in divided doses. If the patient was in combination with the SU therapy, this

Table 1 Clinical data on the patients (mean and range)

Treatment group	n	Age (y.)	Duration of diabetes (y.)	Body weight (kg)	Relative body weight (%)	ESR (mm/h)
Glibenclamide (8 men, 11 women)	19	66.3 (51-77)	9.1 (4-18)	72.1 (57.6-86.6)	116.7 (94.3-131.5)	1
Glipizide (11 men, 4 women)	15	62.9 (53-78)	9.8 (1-16)	77.4 (63.2-101.0)	114.7 (84.7-130.5)	11

during the study. About 50% of the patients had this combination. 2) For a long time on a diet restricted in respect of fat and "fast" carbohydrates. The diet had been investigated, balanced and checked by a dietician several times. 3) Good health, i.e. no clinical symptoms of diabetes. 4) No major changes in glucose homeostasis or body weight in recent months. 5) No acute infections. Normal ESP or if slightly elevated at the same level for a long time. 6) No serious diseases other than diabetes which could be expected to interfere with the study. Drugs such as diuretics and other antihypertensives were kept constant during the study. Three patients, one in the glibenclamide and two in the glipizide group, were dropped from the study owing to intercurrent diseases. The clinical study population is presented in Table 1.

The study was carried out with a double-blind, crossover, double-dummy technique. The 20 patients on glibenclamide and the 20 on glipizide were randomized separately so that with either glibenclamide or glipizide. Thus one half of the patients started with each drug within two months. After 4-6 weeks they switched over to the other drug, each patient thus being his own control. As a blind study was essential, placebo tablets of one drug were given together with the active substance of the other. The dosage was 10 mg of active substance together with breakfast and 4 mg together with the evening meal (at 19.00 p.m.).

Randomizing, loading of tablet containers and coding were performed by the local chemist. Glibenclamide, glipizide and placebo tablets were supplied by Boehringer Mannheim, Mannheim, West Germany, and Carlo Erba Research Institute, Milan, Italy.

During the test period each patient was examined three times: first on entering the study and then after each blind period. Then came to the laboratory on Wednesday, Thursday or Friday in the morning on the fasting state. The study was carried through during Sept.-Dec. and was ended before the Christmas holidays. The following variables were examined: body weight, fasting values of S-glucose, S-insulin, S-haemoglobin, S-triglycerides, S-creatinine, B-haemoglobin and ESR, glucosuria, 24 hours.

One hour after a standardized meal (two sandwiches and 300 ml low-fat (0.5%) milk, about 1760 kJ = 420 kcal (CH 38%)) together with which the relevant SU drug was taken, a new venous blood sample was taken for determination of S-glucose and S-insulin.

Serum was separated from the blood within one hour

and stored at -20°C until analyzed. Separated after deproteinization with a glass method (Boehringer Mannheim, but no CAT) was measured by means of a competitive radioimmunoassay (Phadbas Insulin T-61, Uppsala, Sweden (25)). Urinary glucose was with an o-toluidine method (13). S-haemoglobin was a modification of the method of Frenzel (11) and S-triglycerides according to a modification of Carlson and Wadström (4). The lipids were expressed as relative body weight, percent of "ideal weight" as obtained from a table (18).

The statistical significance of differences was determined by Wilcoxon matched paired signed rank test (unless stated otherwise). The difference was significant for values of  $p < 0.05$ .

## RESULTS

Mean concentrations of the investigated 4-6 weeks after treatment with glibenclamide or glipizide respectively are presented in Table II. A significantly lower fasting glucose after the glibenclamide period was associated with a significantly higher fasting insulin level.

The standardized meal gave a significant insulin level one hour postprandially. The glipizide period associated with a 1.5-fold increase in postprandial blood glucose, although not statistically significant.

The lower blood glucose level, fasting postprandially, after the glibenclamide period was associated with a significantly lower plasma glucose the day before the standard meal. No differences were found in lipid levels. The weight between the two periods did not change during the randomization. One half of the patients did not change drug when they entered the study. In spite of this a significant fall in S-glucose both fasting (from 11.13.5 ± 3.2 mmol/l ( $p < 0.01$ )) and postprandially

## II S-glucose, S-insulin and U-glucose (mean $\pm$ S.D.) in 37 patients 4-6 weeks after a daily dose of 15 mg glibenclamide or glipizide

calculations based on individual differences n.s. = not significant

	S-glucose (mmol/l)			S-insulin (mU/l)			U-glucose (mmol)	n
	Fasting	1 hour	Difference	Fasting	1 hour	Difference		
Glibenclamide	12.5 $\pm$ 3.2	18.2 $\pm$ 3.7	5.7 $\pm$ 1.7	12.7 $\pm$ 7.9	26.1 $\pm$ 18.6	13.4 $\pm$ 12.6	128.5 $\pm$ 11.1 (range 0-45)	37
	14.1 $\pm$ 3.4	19.2 $\pm$ 3.9	5.1 $\pm$ 1.7	11.0 $\pm$ 5.9	29.7 $\pm$ 20.7	18.7 $\pm$ 16.6	182.1 $\pm$ 193.6 (range 0-749)	
	<0.001	<0.05	n.s.	<0.02	<0.01	<0.001	<0.01	

to 18.9  $\pm$  3.8 mmol/l ( $p$  < 0.05) was found at the first and second visit to the clinic in 19 patients. The 24-hour urinary glucose excretion the day before the test did not fall below 74.1  $\pm$  108.4 and 178.7  $\pm$  175.6 mmol respectively.

Side effects including hypoglycaemic reactions and other drug were noted during the study.

### DISCUSSION

The trial was performed on patients with insulin-dependent diabetes who had been followed by a physician at the same outpatient clinic for often for a long time. Standardized medical or dietary treatment (dietitian) medical therapy and diabetic control had been satisfactory prior to the study, guaranteeing as homogeneous patient material as possible. All patients had fasting hyperglycaemia and increased glucosuria despite glibenclamide or glipizide at the recommended maximum dosage (15 mg) but had no clinical symptoms of diabetes

## S-cholesterol and body weight (mean $\pm$ S.D.) in 37 patients 4-6 weeks after a daily dose of 15 mg glibenclamide or glipizide

calculations based on individual differences n.s. = not significant

	S-cholesterol (mmol/l)	S-triglycerides (mmol/l)	Body weight (kg)
Glibenclamide	6.77 $\pm$ 1.28	2.36 $\pm$ 1.14	74.6 $\pm$ 9.5
	6.80 $\pm$ 1.24	2.39 $\pm$ 1.06	74.4 $\pm$ 9.6
	n.s.	n.s.	n.s.

such as thirst, polyuria, tiredness, ketonuria, weight loss. The manifest disturbance in their glucose homeostasis made it impossible to have a placebo period between the two active drug periods, as proposed by the Committee on the Use of Therapeutic Agents of the American Diabetes Association (9).

The duration of each period of active substance was limited to 4-6 weeks, the aim being to carry out a study during the autumn term to avoid the influence of Christmas celebrations. The influence of seasonal variations and a possible deterioration of glucose homeostasis with time was further reduced by performing the study with cross-over technique. To avoid weekend influences on glucose homeostasis, the patients visited the clinic on Wednesday-Friday. To avoid placebo effects of the drugs as well as other psychological effects such as, for example, an unconscious tightening up on the diet or exercise when starting a new drug, the study was performed with a double-blind technique. The active tablets of glibenclamide and glipizide looked different but this was overcome by a double-dummy procedure in which the patients were given the active substance of one drug and placebo tablets of the other. All possible precautions were thus undertaken to eliminate the effects of factors other than the drug on glucose, insulin and lipid homeostasis.

Glibenclamide (20) and glipizide (2, 12, 22) have been shown to be practically completely absorbed. The absorption of glipizide has, however, been reported to be faster, with maximal serum concentrations of the drug at around one hour (12, 23) compared with 2-5 hours for glibenclamide (5, 12, 21). Compared with glibenclamide, the insulin secretion after glipizide given orally in combination with food starts earlier and is of shorter duration (1, 7, 8, 16).

21) Also the effect on the blood glucose concentration is faster after glipizide (1-19). The sustained effect on insulin secretion after glibenclamide is not merely an effect of delayed intestinal absorption as it is found also after intravenous administration of the drug (1). The prolonged effect of glibenclamide on insulin secretion might be responsible for the higher fasting insulin level as well as for the lower fasting blood glucose concentration after the glibenclamide period. A normalization of the morning blood glucose level is often considered very important for glucose homeostasis during the rest of the day. The faster insulin secretion after glipizide would explain the higher serum insulin level one hour after the standardized meal. The higher postprandial insulin level after glipizide gave a marginally lower increase of the postprandial blood glucose concentration but could not overcome the effect of the higher fasting blood glucose level and thus left the patients with a marginally higher blood glucose level even postprandially. The higher 24-hour urine glucose excretion during glipizide therapy indicates that the blood glucose concentration remains on a higher level throughout the day when compared with glibenclamide therapy.

In these patients requiring a high dosage of SU glibenclamide seems to have a somewhat more potent blood glucose lowering effect in the fasting state as well as during the day. The observed marginal differences found may be a matter of non-equipotency even though the drugs were given in amounts generally accepted to be equipotent (24). In an individual case a residual hyperglycaemia despite 15 mg of glibenclamide or glipizide daily

to an increase of the dose to 20-25 mg a day. Both drugs have a very low toxicity (14-17). Clinical experience shows however that weight gains are seldom achieved. The routine dosage of 10 mg with breakfast and 5 mg with evening meal may be changed to more divided dosages especially of glipizide. In a patient with morning hyperglycaemia one dosage may be tried with a late evening meal.

In SU treated patients with normalized glucose homeostasis the faster and shorter insulin secretion after glipizide may be of value for avoiding hyperinsulinaemia as well as hypoglycaemia between meals. This might be of especial importance during weight reduction.

There is no convincing evidence that the degree of secondary failure rate differs between SU drugs.

The earlier onset of effect and shorter duration of insulin secretion after glipizide might have an effect on the  $\beta$ -cell function. On the other hand, chlorpropamide which is even longer acting than glibenclamide has in one study been found to have a tendency to a lower rate of secondary failure compared with glibenclamide (6). A large prospective study will soon be commenced to evaluate whether there is any difference in the secondary failure between short and long acting SU drugs.

The psychological effect of changing therapy is demonstrated by the fact that the patients in accordance with the randomization did not take any active substance when entering the double-blind study. The study had a significantly lower fasting blood glucose level after the first blind period than at the start of the trial. These observations firmly suggest that comparative studies must be performed under controlled conditions.

The lipid concentrations remained unchanged during the study underlining the concept that glibenclamide and glipizide are potent antidiabetic drugs which differ only marginally.

This short term comparative study of glibenclamide and glipizide was focused on short term effects on glucose and insulin homeostasis. The very important long-term effects of diabetes therapy were not investigated. Long-term effects on cardiovascular morbidity and mortality, substances with effects on thrombocyte adhesiveness, thrombolytic aggregation and effects on the fibrinolytic system may achieve great importance.

## REFERENCES

1. Arini D, Abbati R, Orsini G, Parodi A, Bloch K, Datori S & Mandelli M. Pharmacodynamic aspects of two sulphonylurea derivatives glipizide and glibenclamide. *Diabetologia* 1973; 9: 311-17.
2. Balant L, Zahnd G, Gorga A, Scheraga H, Fabre J. Pharmacokinetics of glipizide in patients with renal insufficiency. *Diabetologia* 1973; 9: 331-3.
3. Bengtsson K, Karlberg B & Lindgren H. Acidosis in phenformin-treated diabetes mellitus: a laboratory study. *Acta Med Scand* 1971; 189: 1-10.
4. Carlson L A & Wadstrom L B. Determination of glycosides in blood serum. *Clin Chem Acta* 1959; 5: 1-10.
5. Christ O E, Heptner W & Rumm W. Influence of food on absorption, excretion and metabolism of glipizide. *Diabetologia* 1973; 9: 311-17.

- 11 C labelled HB 419 Horm Metab Res Suppl ad  
1 11 1969
- 12 B & Campbell I Long term comparative  
of gl benclamide and chlorpropamide in the  
diagnosis of onset of diabetes Lancet i 246 1975
- 13 M Lew S A De Mowbray R Boucher  
Jalley N W Nabarro J et al Metabolic and  
cal effects of gl benclamide Lancet i 57 1970
- 14 G Gutierrez A J & Fernandez Cruz A  
cal evaluation of gl pizide in patients with dia  
mellitus Curr Med Res Op n (Suppl) i 61 1975
- 15 ronal by the Committee on the Use of Therapeutic  
n Clinical evaluation of drugs for the treatment  
of Diabetes 13 479 1964
- 16 A Molari E Colombo Pirola L &  
G Gl pizide a new sulphonylurea in the  
treatment of diabetes mellitus Summary of clinical  
experience in 1064 cases Arznei m Forsch 27 1881  
1
- 17 R J & Amador E Serum cholesterol  
measurement based on ethanol extraction and ferric  
sulphuric acid Clin Chim Acta 21 255 1968
- 18 L M Tamassia V & Valzell G  
metabolism and kinetics of the hypoglycemic agent  
pizide in man—comparison with gl benclamide J  
Pharmacol 13 68 1973
- 19 A Helger R & Lang H De Blutzucker  
bestimmung mit o-Toluol in Methode ohne Eisess  
Z Klin Chem 7 14 1969
- 20 G Scholz J Schütz E Czerwek H &  
ank R Toxicity tests of HB 419 in animals  
Conference on the new antidiabetic agent  
14 9 27th to 29th January pp 26–31 1969
- 21 berg W Natvig H Rygh A & Svendsen K  
syde og vektundersøkelser hos voksne menn och  
Tidsskr Nor Lægeforen 76 361 1956
- 22 S del Nevo G Bini P P & Sacchetti G  
pharmacological methods for evaluating a new  
hypoglycemic agent in humans a multistep design  
Arznei m Forsch 21 215 1971
- 23 Mizukami K Miyamoto M Hayashi S  
Kobayashi M Sakura M & Sakaguchi T To  
xikologische Untersuchung von N-4 [7-45 Ch o  
Methoxybenzamide]-Aethyl [Phenyl sulfonyl N C  
clohexylammonium] (HB 419) Arznei m Forsch 19 141  
1969
- 24 Müller R Bauer G Schröder R & Sitt S  
Summary report of clinical investigation of the oral  
antidiabetic drug HB 419 (gl benclamide) Horm  
Metab Res Suppl ad vol 1 88 1969
- 25 Pisan Ceretti A Losi S Orsini G & Emanuel  
A A controlled study of the hypoglycemic and  
sulfonylureic effect of gl pizide and gl benclamide in  
non-diabetic human subjects Arznei m Forsch  
25 675 1975
- 26 Rupp W Christ O & Fulberth W Untersu chung  
en zur Bioavailabilität von Gl benclamide Arznei m  
Forsch 22 471 1972
- 27 Schmidt H & Petrides P Glukose und HB-419  
Konzentration im Blut sowie HB-419-Ausscheidung im  
Urin nach einmaliger oraler Applikation von HB 419  
14 C Arznei m Forsch 19 147 1969
- 28 Schmidt H Schoog M Schweizer H & Winkler  
E Pharmacokinetics and pharmacodynamics as well  
as metabolism following orally and intravenously  
administered C 14-gl pizide a new antidiabetic  
Diabetologia Suppl to 9 370 1973
- 29 Tommasin R Pharmacological activity of gl pizide  
Curr Med Res Opin (Suppl) 1 7 1975
- 30 Valati G Caputo G Mandelli V Pagani G  
Montini M & Sacchetti G Pharmacological studies  
in diabetic patients A comparison of gl pizide and  
gl benclamide J Clin Pharmacol 15 60 1975
- 31 Wide L Axén R & Porath J Radioimmuno sor  
bent assay for proteins Chemical couplings of  
antibodies to insoluble dextran Immunochemistry  
4 381 1967





# Metabolic Effects of Glucocorticoid and Ethanol Administration in Phenformin- and Metformin-Treated Obese Diabetics

O B Schaffalitzky de Muckadell H Mortensen and J Lyngsøe

From Medical Department T and the Department of Clinical Chemistry  
Bispebjerg Hospital Copenhagen Denmark

**ACT** Glucocorticoid administration for 24 h in phenformin treated obese diabetics increased blood lactate and lactate/pyruvate (L/P) ratio to levels higher than those found when only one drug was administered. In one of 10 subjects a metabolic acidosis developed during simultaneous administration of the two drugs. Diabetics treated with phenformin or metformin in equivalent dosages exhibited the highest blood lactate and  $\beta$ -hydroxybutyrate levels during treatment both before and during glucocorticoid administration. Ethanol administration in biguanide treated diabetics resulted in identical increases in blood lactate and L/P ratio during phenformin and metformin treatment. These findings are consistent with the hypothesis that phenformin has a stronger inhibitory effect of glucocorticoid than metformin. This may be one reason why a metabolic acidosis is seen much more often in phenformin than metformin-treated patients.

**Key words:** biguanides, diabetes, ethanol, glucocorticoid.

Acta Med Scand 206 269-273 1979

Findings suggest that many cases of lactic acidosis in phenformin and metformin treated obese diabetics are caused by increased drug accumulation due to decreased hepatic and renal elimination (1). Although increased biguanide accumulation may be a major factor in the development of acidosis, the much more frequent occurrence of this condition in phenformin than metformin treated patients is unexplained and suggests that the two drugs may have different effects on lactate metabolism.

Patients who developed lactic acidosis during intensive therapy have suffered from complications such as pneumonia or coronary occlusion. In these states the glucocorticoid production is

increased and since glucocorticoid administration increases the lactate concentration in blood (1) it is conceivable that the increased glucocorticoid production could contribute to the development of lactic acidosis.

We investigated the metabolic effects of glucocorticoid administration in phenformin treated obese diabetics. In order to compare the metabolic effects of metformin and phenformin we also studied the metabolic changes during glucocorticoid and ethanol administration in patients treated with these biguanides.

## PATIENTS AND METHODS

Fourteen obese patients aged 50-67 years with stable diabetes mellitus treated with biguanides for 1-3 years took part in three separate studies. The patients showed no evidence of hepatic, renal or cardiac disease. They were fully informed of the aim and nature of the investigation before giving their consent to participate. The patients were admitted to hospital, received a diet containing 1300 kcal daily during the study and were allowed to walk freely around in the department. They had breakfast at 08.10, lunch at 12.10 and dinner at 18.10.

### Study I

During the first 4 days of hospitalisation 5 patients received phenformin (Dibelin<sup>®</sup>) capsules of 50 mg at 08.00, 12.00 and 18.00. Phenformin was not administered on the 5th day. On the 4th and 5th day hydrocortisone succinate (Solu-Cortef<sup>®</sup>) corresponding to 7 mg hydrocortisone was administered intravenously every hour. A preliminary study showed that this dosage regimen results in approximately a doubling of plasma cortisol. During the 3rd, 4th and 5th day at 18.00 and 24.00 arterial blood was drawn for determination of lactate, pyruvate (3), glucose (glucose oxidase method),  $\beta$ -hydroxybutyrate (4), standard bicarbonate and pH.

### Study II

A cross over study was performed in 5 patients. One week before and during their stay in hospital the patients received phenformin (Dibelin<sup>®</sup>) or metformin (Glucophage<sup>®</sup>).

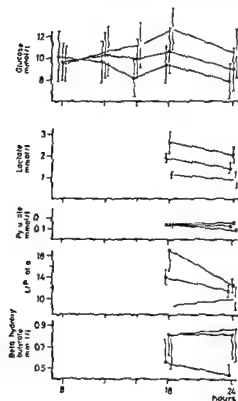


Fig. 1 Metabolic concentration during three consecutive days in 5 obese diabetics treated with phenformin+hydrocortisone succinate (O) and cortisone succinate (x)

### Statistical analysis

	Glucose	Lactate	Pyruvate	L/P	$\beta$ hydroxy butyrate
Phenformin ~ phenformin + steroid	N S	$p < 0.05$	N S	$p < 0.05$	N S
Steroid ~ phenformin + steroid	$p < 0.05$	$p < 0.02$	$p < 0.02$	$p < 0.02$	N S
Phenformin ~ steroid	N S	$p < 0.01$	$p < 0.01$	$p < 0.05$	N S

00, 12 00 and 18 00 daily in doses of 50 mg and 1 000 mg, respectively. Arterial blood was drawn at 12 00, 00, 24 00 and 08 00 on the first and second day of hospitalisation. Hydrocortisone xanthogenate (Solvisat®) corresponding to 7 mg hydrocortisone was administered intravenously every hour during the second day, blood samples being drawn as on the first day.

After the first period of investigation the medication was changed to the other biguanide preparation. After one week's treatment the procedure was repeated. Three patients were treated with phenformin and two with metformin during the first period of investigation.

### Study III

Four patients were examined in a cross-over study. Phenformin or metformin was administered as in study II. After an overnight fast an indwelling catheter was inserted into the left femoral or brachial artery. The catheter was flushed every 5th min with 5 ml isotonic saline. The patients ingested 30 g ethanol in a volume of 150 ml within 1

min. Arterial blood was drawn 15 and 1 min before, 60, 75, 90, 105, 120 min after ethanol ingestion.

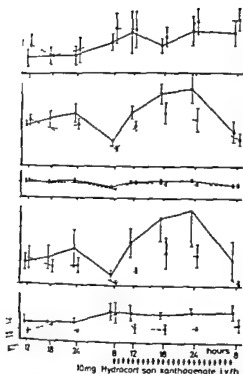
### Statistics

Results are given as mean  $\pm$  S.E.M. Student's *t*-test for paired data was used if not otherwise indicated.

## RESULTS

In phenformin-treated obese diabetics corticoid administration resulted in an increase in lactate and lactate/pyruvate (L/P) ratio. After continuation of phenformin administration the lactate concentration increased as expected, but pyruvate and L/P ratio fell to values those found when phenformin alone was administered (Fig. 1).

Phenformin treatment resulted in significant



Blood metabolite concentrations in phenformin and metformin-treated (■) obese diabetics before and after hydrocortisone xanthogenate administration

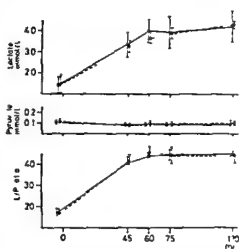


Fig 3 Blood metabolite concentrations in phenformin (□) and metformin treated (■) obese diabetics before and after ethanol administration

glucose values was found during treatment with the two biguanide preparations. However the majority of the blood glucose values in the metformin period were higher than in the phenformin period and real difference between the two periods cannot be excluded (Fig 2).

Plasma  $\beta$  hydroxybutyrate was significantly higher during treatment with phenformin than with metformin ( $p < 0.005$  three way analysis of variance) (Fig 2).

Administration of ethanol resulted in an equal increase in blood lactate and L/P ratio during treatment with phenformin and metformin (Fig 3).

## DISCUSSION

The present investigation has shown that biguanide and glucocorticoid have a synergistic action on blood lactate concentration and L/P ratio. Recent studies have shown an increase in blood concentrations of lactate, alanine and glycerol during biguanide therapy (18) and these authors suggest that this effect of biguanide is caused by an inhibitory action on gluconeogenesis. This hypothesis is supported by studies in animals (1, 8, 17) and humans (5, 10, 16).

Since glucocorticoid administration induces an increased mobilisation of gluconeogenic precursors from muscle (12) the additive effect of the two drugs can be explained as a result of increased mobilisation and decreased utilisation of gluconeogenic precursors.

In accordance with previous investigators (18) we found increased L/P ratio during therapy with biguanides suggesting that the drugs interfere with hepatic cellular oxidation and increase the cytosolic NADH/NAD ratio. Since a similar effect of glucocorticoids has been reported (19) the additive effect of biguanides and steroids on the L/P ratio is consistent with this theory.

The changes in blood lactate and L/P ratio during combined administration of biguanide and glucocorticoid follow the same pattern although much less pronounced as in biguanide associated lactic acidosis. In only one of our 10 patients the increase in lactate was accompanied by a reduction of standard bicarbonate to values below normal. However, in disease states as cardiac infarction and infections often associated with lactic acidosis in biguanide treated patients the production of both glucocorticoids and catecholamines is increased. Catecholamines increase blood lactate (6) and lactic acidosis has been reported in pheochromocytoma (14). Therefore it seems probable that the combined effect of increased glucocorticoid and catecholamine levels on lactic acid metabolism contribute to the lactic acidosis seen in biguanide treated diabetics during complicating diseases.

Higher blood lactate L/P ratio and  $\beta$  hydroxybutyrate values were found during phenformin than metformin treatment both before and during glucocorticoid administration. These findings correspond to those reported in previous studies in diabetics not treated with glucocorticoid (9, 18).

Our results rise the question whether the differences in blood metabolite concentrations during treatment with phenformin and metformin are induced by the chosen dosages. Our data do not include this possibility. However, in a recent study (8) a dose of metformin smaller than that used by us had the same hypoglycemic effect as our dose of phenformin. Therefore our findings suggest that when the two biguanides are used in equipotent dosages phenformin causes the highest blood lactate and L/P ratio. This probably reflects a stronger inhibitory effect of phenformin on hepatic cellular oxidation and gluconeogenesis. The higher  $\beta$  hydroxybutyrate and  $\beta$  hydroxybutyrate/acetoacetate ratio during phenformin than during metformin treatment found by us and other authors (18) support this hypothesis.

Administration of ethanol during treatment with the two biguanides caused identical increases in

blood lactate and L/P ratios. Ethanol is a strong inhibitor of gluconeogenesis and these changes may result from a common inhibitory effect of biguanides and ethanol on this process.

That no differences were found between ethanol induced metabolic changes during metformin and phenformin treatment may be explained by a much stronger inhibition of gluconeogenesis by ethanol than by the biguanides.

## ACKNOWLEDGEMENT

This work was supported by a grant from King Gustaf X Foundation.

## REFERENCES

- 1 Altschuld R A & Kruger F A. Inhibition of hepatic gluconeogenesis in guinea pig by phenformin. *NY Acad Sci* 148: 612, 1968.
- 2 Assan R, Heuclin C, Girard J R, Le Maréchal J R. Phenformin induced lactic acidosis in diabetic patients. *Diabetes* 24: 791, 1975.
- 3 Bergmeyer H U. Methods of enzymatic analysis, pp 266-270, 253-259. Academic Press, New York, 1963.
- 4 Bitsch V. A modification of the Glibbard & Wark method for determination of D-beta-hydroxybutyrate. *Clin Chim Acta* 38: 471, 1972.
- 5 Bottermann P, Schweigert U & Emler L. Untersuchungen zum Wirkungsmechanismus von Bufornin mit Hilfe triierter Glucose bei Stoffwechselgesunden Personen. *Med Klin* 71: 1423, 1976.
- 6 Christensen N J, Alberti K G M M, Brandsborg O. Plasma catecholamines and the substrate concentrations. Studies in insulin induced hypoglycemia and after adrenaline infusions. *Exp Clin Invest* 5: 415, 1975.
- 7 Conlay L A, Karam J H, Matton S P, Loewenstein J E. Serum phenformin concentrations in patients with phenformin associated lactic acidosis. *Diabetes* 26: 628, 1977.
- 8 Cook D E, Blair J B & Lardy H A. V & action of hypoglycemic agents. V. Studies of phenethylbiguanide in isolated perfused rat liver. *Biol Chem* 248: 5272, 1973.
- 9 Czyzyk A, Lao B, Bartozewicz W, Szczepanik Z. Comparative evaluation of the effect of antidiabetic biguanide derivatives on the blood lactate level. *Diabetologia* 9: 64, 1973.
- 10 Dietze G, Wicklmayer M, Mehner H, Czernig H & Henfling H G. Effect of phenformin on the metabolic balance of gluconeogenic substrates in man. *Diabetologia* 14: 243, 1978.
- 11 Henneman D H & Bunker J P. The form of intermediary carbohydrate metabolism in Cushing's syndrome. *Am J Med* 26: 34, 1957.
- 12 Ingle D J, Prestrud M C & Nezamis J E. Ethanol

- renalectomy upon level of blood amino acids in a castrated rat. *Proc Soc Exp Biol Med* 67: 371
- d F & Lavauzelle M. Acidose lactique et uriques. Etat actuel de la question en France. *Ann Diabetol Hotel Dieu* 36: 1977
- r U, Mall Th, Walter M, Bertel O, Sch J M & Ritz R. Pheochromocytoma with acidosis. *Br Med J* 11: 606, 1978
- D, Schulling R M & Eggstein M. Lactic acidosis in guanidine-treated diabetics. A review of cases. *Diabetologia* 14: 75, 1978
- see J & Trap-Jensen J. Phenformin induced hypoglycemia in normal subjects. *Br Med J* 1969
- 17 Meyer F, Ipaktschi M & Clauser H. Stimulation of gluconeogenesis by bicarbonate. *Diabetologia* 13: 203, 1967
- 18 Natrass M, Todd P G, Hinks L, Lloyd Alberti K G M M. Comparative effects of phenformin, metformin and glibenclamide on metabolic rhythms in maturity-onset diabetes. *Diabetologia* 13: 145, 1977
- 19 Yelding K L & Tomkins G M. Inhibition of enzymic oxidation of DPNH by steroid hormones. *Proc Natl Acad Sci USA* 45: 1730, 1959



# Clinical Significance of Abnormal Heterogeneity of Transferrin in Relation to Alcohol Consumption

Helena Ståhl, Stefan Borg and Christer Allgulander

From the Department of Neurology and Karolinska Institute Clinical Department of Alcohol and Drug Research, Karolinska Hospital, Stockholm, Sweden

**ABSTRACT** An abnormal microheterogeneous form of serum transferrin with a higher isoelectric point than the normal main component was detected by means of isoelectric focusing and immunofixation in 98 alcoholic patients, 22 patients with liver diseases and 100 controls. Its relation to alcohol consumption and prolonged ethanol intake was studied in volunteers. The abnormal transferrin component was found to be a sensitive indicator of prolonged high alcohol ingestion and was observed in patients with an admitted consumption of about 60 g ethanol/day and normalized after 4 days of abstinence. It occurred in 1% of the controls and in none of the cases with liver diseases or current alcohol abuse. There is evidence of a fall in aspartic acid content in the abnormal transferrin. A similar change has been found in a number of glycoproteins. This test may be a useful and reliable tool for the detection of chronic alcohol consumption.

**Key words:** alcoholism, liver diseases, transferrin, serum isoelectric focusing, immunofixation, serum glutamyl transferase.

biochemical abnormalities may be found in patients with excessive alcohol intake and some are often used as markers in the diagnosis of alcoholism. One commonly recommended investigation of the gamma glutamyl transferase activity in serum (SGT) which has been found to be increased in 54-88% of chronic alcoholics (7-9, 11, 12, 14, 15, 17). Increases in serum lipoproteins can be observed in 40-87% of alcoholics (6, 7) and elevated serum iron is also the rule in association with alcohol intake (4, 5, 23, 24). These and most other laboratory tests are, however, unsatisfactory because of

their lack of specificity. For example, the serum glutamyl transferase activity is usually normal even also in liver diseases of non alcoholic origin.

Recently Shaw et al. (15, 16) reported an increased quotient between alpha amino butyric acid and leucine in plasma of chronic alcoholics. This test gave positive results in 57% of the controls and if it was combined with determination of the serum gamma glutamyl transferase activity, a positive diagnosis was obtained in 81%. The value of the alpha amino butyric acid/leucine quotient can, however, not yet be considered to be established (10).

During the examination of the cerebrospinal fluid and serum proteins by means of analytical isoelectric focusing in patients with neurological diseases it was observed that several patients with alcoholic cerebellar ataxia had a qualitative abnormality of the serum transferrin (19, 22). In a subsequent report this transferrin change was found in 15 out of 16 alcoholics and was reversible within 7-14 days of alcohol abstinence. The abnormality consists of a qualitative alteration of the microheterogeneity of transferrin with the appearance of a marked more positively charged component having an isoelectric pH of 5.7 (21).

The purpose of this investigation was to determine 1) the occurrence of this transferrin abnormality in alcoholics in relation to the daily alcohol intake, 2) its specificity for alcoholism as compared to patients with different liver diseases, 3) its sensitivity by examination of healthy volunteers during alcohol ingestion.

## STUDY POPULATION

### Controls

These were 100 volunteers considered healthy according to history and physical examination. In no instance was



Table I Clinical data and results of isoelectric focusing of serum and S-GT determination in 100 controls, 98 alcoholic patients and 22 patients with liver diseases

	N	Age range (y)	Sex		% with abnormal transferrin	% with increased S-GT (>10 µkat/l)
			♂	♀		
Controls	100	19-65	50	50	1	-
Alcoholics	98	22-75	78	20		
Group I	26	24-75	19	7	8	8
Group II	20	34-74	20	0	25	42
Group III	20	22-63	12	8	75	47
Group IV	32	27-67	27	5	81	77
Liver diseases	22	36-72	9	13	0	84

Group I=no admitted alcohol consumption for 3 weeks group II=an admitted average of 7-20 g alcohol/day the previous week group III=20-60 g alcohol/day during the previous week group IV=>60 g alcohol/day the previous week None of the patients with liver diseases had any current alcohol abuse

any regular excessive alcohol consumption suspected. No one was on any drug therapy apart from one female who used an oral contraceptive. The age range was 19-65 years and 50 were males and 50 females (Table I).

Three of the male volunteers aged 29-34 years participated in the experiment involving ingestion of a single high ethanol dose. Eight of the controls, five females and three males aged 19-32 years volunteered for the experiment involving daily consumption of ethanol over a period of 7 days (see below). These experiments were approved of by the Ethical Committee of the Karolinska Institute.

#### Alcoholic patients

Ninety-eight patients treated at the Karolinska Institute Clinical Department of Alcohol and Drug Research were examined. Seventy-eight were males and 20 females with in the age range 22-75 years. All patients fulfilled the criteria of alcohol dependence according to WHO (28). Alcoholism was estimated to have lasted for 4-40 years. The patients were divided into four groups according to the daily average of the admitted amount of alcohol consumed during the previous week in groups II-IV and during the previous three weeks in group I (Table I). The

11 histories revealed three patients with biopsy verified cirrhosis of the liver, three with clinical and laboratory signs of hepatic insufficiency, two with diabetes mellitus, five with hypertension and five with heart disease.

Table II Diagnoses of 22 patients with liver diseases without current alcohol abuse

	N
Laennec's cirrhosis	5
Primary biliary cirrhosis	3
Chronic active hepatitis	5
Haemochromatosis with cirrhosis	2
Fatty liver	1
Allergic hepatopathy	1
Metastases	2
Primary hepatic carcinoma	1
Hepatopathy NUD	2

Seven subjects had previously had alcoholic delirium. 16 had suffered from epileptic seizures before abstinence and nine had a previous history of drug abuse.

#### Patients with liver diseases without current alcohol abuse

Twenty-two patients with different liver diseases, provided by B. Angelin, Department of Internal Medicine, Serafimerlasarettet (Stockholm) were examined. There were 13 males and 9 females aged 36-77 years. All those with liver malignancy were outpatients in clinical condition. The diagnoses were based on clinical and laboratory evaluation and in all cases also on liver biopsy material (H. Glaumann, Department of Pathology, Huddinge Hospital, Stockholm). In all instances there was no current alcohol abuse admitted. Excepted and apart from the five patients with Laennec's cirrhosis, no one gave any history of previous alcohol abuse (Table II).

## METHODS

#### Sampling

Serum samples were taken in the morning in all subjects fasting. From the alcoholic patients in group I the samples were collected either during current alcohol abuse or at the latest on the third day after cessation of drinking. For isoelectric focusing the samples were analyzed immediately or frozen and stored at -20°C the most 6 months before analysis (21).

#### Isoelectric focusing

Analytical isoelectric focusing was carried out in 1% of polyacrylamide gel essentially according to Verwey (26, 27) as modified by Kjellin and Vesterberg (28, 29). The gel concentrations were T=7.5% and C=3%. Sucrose was present in 12% (w/v) and 0.0005% (w/v) was used as initiator of the polymerization of the gels. The pH gradient was in the range 3.5-11.0 and the final Ampholine (LKB) was

concentration was 1% (w/v). The electrode distance was 8.5 cm. Each serum sample was diluted 1:10 in distilled water and thereafter a sample of 30 µl was placed on a small piece of surgical lint (Robinson, Chesapeake, England) and placed centrally on the gel surface. Ten samples were analyzed on the same gel. The electrofocusing cell type F and a constant water supply P 101 were obtained from AB Analytiska, Umeå, Sweden. The maximal voltage was 100 kV at a maximal wattage 40 W. The separations were run for 25 min. The pH measurements were performed with a surface electrode type LOT 403-30-M9 (Institute for Surface Chemistry, Zurich, Switzerland) at +20°C (26). Staining with Brilliant Blue R 250 (ICI, Manchester, England) and destaining were carried out according to Vesberg (26).

#### Immunofixation

Immunofixation following isoelectric focusing was carried out as described by Ståhl (20). Two identical gels of the same samples were analyzed simultaneously. After isoelectric focusing, thereafter one gel was used for immunofixation, the second being stained for control purposes. For immunofixation the samples were diluted 1:30 or 1:40 and 10 or 20 µl thereof were used. After completion of the focusing 25 µl/cm<sup>2</sup> of a monospecific antiserum against human serum transferrin or IgA (Dakopatts, Copenhagen, Denmark) was applied to the surface of the polyacrylamide gel at the area where these proteins are known to be located. Incubation was carried out at room temperature for 40-60 min. The gels were then washed and destained (20).

#### Enzyme experiments

Normal and pathological patient sera were examined for isoelectric focusing and direct immunofixation. Antisera against transferrin after complete digestion with neuraminidase (1 U/ml from Vibrio cholerae, Behringwerke, West Germany) (18). Five µl of serum were incubated with 40 µl neuraminidase at +37°C for 2 hours and diluted with distilled water to 1:20 for isoelectric focusing and to 1:30 and 1:40 for immunofixation.

#### Determination of the S/GT activity

Serum samples from 89 of the alcoholic patients, 19 of the controls with liver diseases and the eight controls participating in the experiment with daily ethanol intake (see above) were examined on the same days as samples for isoelectric focusing were taken. The S/GT activity was determined according to Szasz et al. (25) with the use of Technicon SMA 12/60 from Boehringer Mannheim GmbH, Mannheim, West Germany (Laboratory of Clinical Chemistry, Karolinska Hospital, Stockholm). The reference value of the laboratory was <1.0.

#### Administration to healthy volunteers

The volunteers were all medical personnel at the Karolinska Institute Clinical Department of Alcohol and

Drug Research. They had abstained from alcohol for one week before the experiments were kept on a normal diet throughout the trial and had agreed not to use alcohol beverages during the experiments.

Three healthy males participated in a trial involving ingestion of one single dose of 1.8 g ethanol/kg b.wt. in the form of Scotch whisky at noon. Serum samples for isoelectric focusing were collected on the morning before the trial and on the first and second mornings after ethanol intake.

Another eight volunteers participated in an experiment involving daily ingestion of 0.60 g ethanol/kg b.wt. (95.5% ethanol diluted with pure fruit juice) every afternoon for seven days. The daily amount ingested corresponds to about 40 cl wine. Serum samples for isoelectric focusing and S/GT determination were taken on the morning before the trial from all eight subjects and thereafter every morning for 8 days and on the 11th day. From two of the subjects with positive results on isoelectric focusing it was possible to collect samples also on the 13th, 14th and 18th days.

#### Statistical method

Fisher's exact test was used to compare the frequency of the abnormal transferrin component and increased S/GT activity between the four patient groups. The same test was used to make the comparison between the presence of the transferrin alteration and elevated S/GT values within each group.

## RESULTS

### Controls

The normal protein pattern on isoelectric focusing is shown in Fig. 1A. In only one individual (male, aged 32 years) was the transferrin abnormality present which represents 1% in the control material (Table 1).

### Alcoholic patients

B and F in Fig. 1 show the transferrin abnormality after isoelectric focusing and its specific identification with direct immunofixation. It consists of a selective and marked increase of a microheterogeneous component with a higher isoelectric pH (pI 5.7) than the normal main band of this protein (pI 5.4) (21). None of the other six components of transferrin shows any corresponding increase. In the serum of the patient shown in the figure there is also a faint additional even more cathodal band at the pI of 5.9 which has been found in one quarter of alcoholic patients (21).

The results from desialylation with neuraminidase of normal and patient sera are exemplified by C-D and G-H in Fig. 1. After complete removal of the sialic acid the difference between normal

The 8% positive results for both the transferrin component and elevated S/GT activity among patients in group I is probably an expression of undiminished alcohol intake. The slightly but not significantly higher frequency of the transferrin abnormality in group II may have the same cause or be due to a remaining change from higher consumption during the preceding week. This may also explain the somewhat but not significantly higher frequency of increased S/GT values than the abnormal transferrin band in group II, since raised values return slowly to normal levels within 2–3 weeks of abstinence (12). Further, the S/GT activity may increase after intake of relatively large amounts of alcohol during a short time (3, 14).

Some other proteins,  $\alpha_2$  macroglobulin, haptoglobin, C'3 complement and IgA have components in close proximity to the abnormal transferrin band and may therefore impose problems if increased (18–20). Direct immunofixation following isoelectric focusing using antibodies against transferrin is then a convenient means to establish the nature of the protein band (Fig. 1E–F). In some samples lipoproteins may be found in the same region. These are usually easy to identify, since they focus badly, often with the appearance of zigzag bands, and are seen on the surface layer of the gel of the type used here. In doubtful cases the lipoproteins can be removed quickly by delipidation according to Cham and Knowles (1) (Stibler unpublished).

The cause of the change of the transferrin has so far not been established. A purely quantitative explanation has previously been excluded (21) and is contradicted by the fact that the alteration comprises just one component, at the position of which there is normally only one of the minor bands of the protein. The results of desialylation (Fig. 1G–H) speak in favour of a reduced sialic acid content in the abnormal component. The remaining difference from normal sera after desialylation reported on crossed immunoelectrofocusing (21) may be due to technical difficulties with that method, differences in the amount of diffused protein from the polyacrylamide gel to the agarose gel, or to errors concerned with the low mobility of proteins isoelectric around pH 6 in the buffer pH used. The direct immunofixation technique is more sensitive and more reliable in the present situation, since it is not afflicted with these sources of error (20). A low sialic acid content might be due to a defective sialy-

lation by sialyl transferase during synthesis, or to normal release of newly synthesized but not sialylated transferrin to increased peripheral sialic acid, or to a defect in the elimination of acid deficient transferrin (2). Since no corresponding qualitative change has been observed in other glycoproteins studied, this defect appears to affect transferrin in a more selective way.

Investigations are currently being carried out to further study the specificity of the transferrin abnormality for alcoholism, e.g. in patients with malabsorption and other types of addiction; furthermore, a method to make possible a quantitative estimation of the abnormal component in relation to the main one is being developed.

## ACKNOWLEDGEMENTS

Financial support was given by the Karolinska Institute and the Swedish Multiple Sclerosis Society.

## REFERENCES

1. Cham B & Knowles B. A solvent system for the detection of plasma or serum without protein precipitation. *J Lipid Res* 17: 176, 1976.
2. Clamp J. Structure and function of glycoproteins. In: *The plasma proteins: structure, function, genetic control*, vol. II (ed. F. W. Putnam), p. 11. Academic Press, New York, 1975.
3. Freer D & Statland B. The effects of ethanol (g/kg body weight) on the activities of 9 enzymes in sera of healthy young adults. Immediate term effects. *Clin Chem* 23: 810, 1977.
4. Herbert V & Tisman G. Hematology and alcohol. *Ann NY Acad Sci* 257: 307, 1975.
5. Hillman R. Alcohol and hematopoiesis. *Ann NY Acad Sci* 252: 297, 1975.
6. Johansson B G & Laurell C B. Distribution of serum alpha lipoproteins after alcoholism. *Scand J Clin Lab Invest* 23: 731, 1969.
7. Johansson B G & Medhus A. Increase in alpha lipoproteins in chronic alcohol abuse. *Acta Med Scand* 195: 273, 1974.
8. Kjellin L G & Vesterberg O. Isoelectric focusing of CSF in neurological diseases. *J Neurol Sci* 1974.
9. Kontinen A, Hartel G & Louheva A. Serum enzymes in chronic alcoholics. *Scand J Clin Lab Invest* 23: 257, 1970.
10. Mezey E. Ratio of plasma alpha amino acid to leucine in alcoholism. *Gastroenterology* 75: 742, 1978.
11. Rollason J G, Pincherle G & Robinson D. gamma glutamyl transpeptidase in relation to consumption. *Clin Chim Acta* 79: 75, 1977.
12. Rosalki S & Rau D. Serum gamma glutamyl

ase activity in alcoholism *Clin Chim Acta* 1977

19 Burg A M, Goldberg J A & Pineda E P. gamma-glutamyl transpeptidase activity in biliary pancreatic disease *Gastroenterology* 1963

20 C. Heffelfinger R & Childers D M. Gamma-glutamyl transpeptidase and the alcoholic response to abstinence *Ann Clin Lab Sci* 1976

21 S. Lue S L & Lieber C S. Biochemical use of the detection of alcoholism. Comparison of alpha-amino-n butyric acid with other available *Alcoholism Clin Exp Res* 2:3 1978

22 S. Stummel B & Lieber C S. Plasma amino-n butyric acid/leucine. A biochemical of alcohol consumption. Application for the diagnosis and assessment of alcoholism. In *Currents in alcoholism* vol 1 (ed F Seitz) p 17. Grune and Co. New York 1976

23 G. & Wadstein J. Amylase hepatic enzymes rubin in serum of chronic alcoholics *Acta Med Scand* 101:53 1977

24 H. The normal cerebrospinal fluid proteins studied by means of thin layer isoelectric focusing and immunoelectrofocusing *J Neurol Sci* 1978

25 isoelectric focusing of the cerebrospinal fluid pro-

teins in degenerative diseases of the central nervous system. Thesis. Karolinska Institute. Stockholm 1978

26 — Direct immunofixation after isoelectric focusing. A improved method for identification of cerebrospinal fluid and serum proteins *J Neurol Sci*. In press 1979

27 Stibler H, Allgulander C, Borg S & Kjellin K G. Abnormal microheterogeneity of transferrin in serum and cerebrospinal fluid in alcoholism *Acta Med Scand* 204:49 1978

28 Stibler H & Kjellin K G. Isoelectric focusing and electrophoresis of the CSF protein in tremor of different origins *J Neurol Sci* 70:269 1976

29 Straus D. Hematologic aspects of alcoholism *Semin Hematol* 10:183 1973

30 Sullivan L & Herbert V. Suppression of hematopoiesis by ethanol *J Clin Invest* 43:2048 1964

31 Szasz G, Weimann G, Stahler F, Wahlefeld A W & Persijn J P. New substrates for measuring gamma glutamyl transpeptidase activity *Z Klin Chem Klin Biochem* 12:228 1974

32 Vesterberg O. Isoelectric focusing of proteins in polyacrylamide gels *Biochim Biophys Acta* 257:11 1972

33 — Isoelectric focusing of proteins in thin layers of polyacrylamide gel *Sci Tools* 20:22 1973

34 WHO Technical Report Series 273:3 1964



## Free Light Chains of Immunoglobulins in Amyloidosis

J. Solling and K. Solling

From Department of Medicine C, Aarhus Kommunehospital, Aarhus, Denmark

LACT Monomeric (M) and dimeric (D) forms of light chains in serum have been measured by a radioimmunoassay in eight patients with amyloidosis without monoclonal proteins. Significant elevated concentrations of D lambda chains were demonstrated in two of four patients with AL amyloidosis. The two patients had a significantly increased D/M ratio of both kappa and lambda chains. One patient with localized AL amyloidosis and normal concentration of monomeric lambda light chains had an abnormal fragment of lambda chains. A low kappa/lambda ratio was found in patients with localized amyloidosis. Four patients with secondary amyloidosis and renal insufficiency had increased amounts of free light chains. The concentration of light chains and the D/M ratio in this group corresponded to the impairment of renal function.

*Key words:* immunoglobulin light chains, amyloidosis.  
Acta Med Scand 206: 293-287, 1979.

Immunoglobulin light chains may be both of immunoglobulin and non-immunoglobulin origin (1-4, 15). Light chains of immunoglobulins are presumed to be one of the proteins constituting the amyloid fibrils (5-7). Jones proteins have been shown to be the major component of amyloid fibrils in a patient with plasma cell dyscrasia (14). The source of the amyloid fibrils in patients without monoclonal proteins is unknown. Kappa and lambda light chains of immunoglobulins or polymeric forms of light chains in amyloidosis may be of pathogenetic significance. In the present study we have used a sensitive radioimmunoassay for light chains to investigate the concentrations of light chains in eight patients with amyloidosis.

## STUDY POPULATION

Eight patients had localized amyloidosis limited to the gastrointestinal tract and no coexisting diseases (3, 6, 7). Seven patients had secondary amyloidosis; three had

amyloidosis secondary to rheumatoid arthritis and one had amyloidosis secondary to tuberculosis (7). Patients with monoclonal proteins on immunoelectrophoresis (Scheidegger) were excluded; this method detects monoclonal proteins at concentrations above 1 g/l. All patients with primary amyloidosis had serum creatinine below 1.3 mg/100 ml and no proteinuria. The patients with secondary amyloidosis had amyloid deposits in the kidneys with proteinuria and decreased creatinine clearance.

As controls we investigated serum from 11 patients with rheumatoid arthritis (six seropositive, four seronegative) and one juvenile arthritis, six patients with tuberculosis (three with active tuberculosis and three with previously treated tuberculosis) and six normal individuals.

## METHODS

The diagnosis of amyloidosis was made on biopsy material. The amyloid showed green birefringence with Congo red under polarized light.

Polymeric forms and split products of free light chains were isolated by gel filtration using a Sephadex G 100 SF column measuring 140 x 1.5 cm. The concentrations of light chains in each fraction were measured by a sensitive radioimmunoassay as previously described (10, 11, 12). The total amount of monomeric and dimeric light chains was calculated by summation of the respective fractions. The molecular weight was estimated by markers of radio-labelled lambda chains. Non-absorbed broadly reactive antibodies against kappa and lambda Bence Jones proteins were used. This was possible because the regular immunoglobulins were separated from the light chains by gel filtration.

## RESULTS

On gel filtration on Sephadex G 100 the free light chains appeared after intact immunoglobulins in two peaks with molecular weight about 44 000 and 22 000, i.e. as dimers (D) and monomers (M) (Fig. 1). Higher polymeric light chains (tri- or tetramers) were demonstrated as a small peak between intact immunoglobulins and dimeric light chains. The total

*Abbreviations:* M = monomeric light chains, D = dimeric light chains.

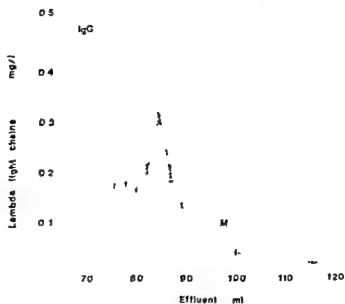
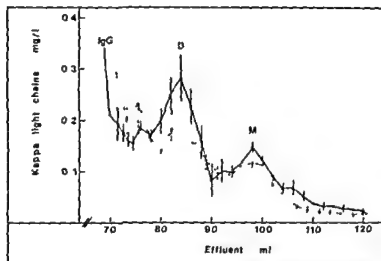


Fig. 1 Mean values of kappa and free light chains after gel filtration on Sephadex G 100 SF in four patients with localized amyloidosis (—) and six normal individuals (---). Vertical lines represent standard error.

amount of dimeric and monomeric kappa and lambda light chains in serum is shown in Table 1.

In the group with localized amyloidosis two of the four patients had elevated concentrations of D lambda chains when compared to normals (*t*-distribution). All patients had normal concentrations of kappa chains and M lambda chains. The concentrations of the tri- or tetrameric chains could not be precisely quantitated due to contamination of intact immunoglobulins. Patient 4 with normal concentrations of M and D light chains had a small abnormal peak appearing after the M light chains (Fig. 2). This peak represents fragments of kappa and lambda light chains.

Two patients (nos. 2 and 3) had significant elevated D/M ratio of both kappa and lambda chains. The mean D/M ratio of kappa chains in localized amyloidosis was  $1.6 \pm 0.5$  (S.D.) compared to  $1.2 \pm 0.2$  (S.D.) in the six normal individuals. The mean D/M ratio of lambda chains was  $3.1 \pm 0.5$  (S.D.) compared to  $2.7 \pm 0.7$  (S.D.) in the six normal individuals. Both these differences are significant (Mann-Whitney rank sum test). The kappa/lambda ratio in localized amyloidosis was  $0.87$  compared to  $1.05$  in the six normal individuals. The difference is not significant (Mann-Whitney test).

Patients with secondary amyloidosis had significantly increased mean values of kappa and lambda

Measurements of M and D free light chains (Lc) of IgG type in 4 patients of amyloidosis and 4 patients with secondary amyloidosis

	Pat no	Kappa Lc (µg/ml)				Lambda Lc (µg/ml)			
		M	D	M+D	D/M	M	D	M+D	D/M
ad	1	41	56	97	1.4	29	68	97	2.4
		36	67	103	1.9	18	107	125	5.9
	3	41	81	122	2.0	30	133	163	4.4
	4	29	26	55	0.9	11	34	45	3.1
		37	58	94	1.6	22	86	108	3.9
my		06	23	28	0.5	09	44	50	1.5
	5	176	191*	367	1.1	29	174	203	6.0
	6	97	101*	198	1.0	14	154	168	11.0
	7	120	189*	309	1.6	28	314	362	11.9
	8	66	87*	153	1.3	16	82	98	5.1
f6 normal		115*	142*	257	1.3	22	186	208	8.5*
		46	56	98	0.3	08	106	111	3.4
		37	45	82	1.2	21	57	78	2.7
		09	14	23	0.2	07	16	21	0.7

±

in serum (Mann-Whitney rank sum test) concentrations of kappa and lambda chains in were inversely correlated to the creatinine. Both M and D kappa chains were elevated only D lambda chains were elevated of four patients. The D/M ratios of kappa chains were  $1.3 \pm 0.3$  (S.D.) and  $8.5 \pm 3.4$ . The corresponding values in anephric patients were  $1.0 \pm 0.3$  and  $6.9 \pm 3.4$  (S.D.) (10, 11). Differences are insignificant. The kappa/lambda was 1.74 and did not differ significantly from normal.

Mean value of free kappa light chains in 11 patients with rheumatoid arthritis was  $10.2 \pm 4.2$  µg/ml serum and of lambda chains  $6.6 \pm 3.3$  µg/ml. One patient with rheumatoid arthritis increased values of both kappa and lambda and one patient had increased values of only chains. Patients with tuberculosis had normal values of kappa light chains  $10.1 \pm 3.5$  (S.D.) serum and of lambda chains  $7.1 \pm 1.3$  (S.D.). None of the mean values differed significantly from normal values (Mann-Whitney rank sum

test). Patients with localized amyloidosis. None of the patients had monoclonal immunoglobulins detectable by immunoelectrophoresis (Schedegger). Chemical studies have shown that the main protein component of purified amyloid fibrils in primary amyloidosis and localized amyloidosis is a whole light chain or the amino terminal variable fragment of a light chain (4, 5, 7, 9). Thus circulating light chains of immunoglobulins may be of pathogenetic significance in the deposition of amyloid fibrils in primary and localized amyloidosis. Free light chains have however never before been measured in serum from patients with primary and localized amyloidosis probably due to the rather insensitive methods generally used for measurements of light chains.

Glenner and Page (4) isolated from a patient with primary amyloidosis a serum protein with antigenic determinants in common with both amyloid fibrils and lambda Bence Jones protein. The concentration of this serum protein was estimated to be less than 0.1 mg/ml and the molecular weight about 90,000.

The demonstration of such small amounts requires a sensitive radioimmunoassay. The detection limit for our assay is 0.007 mg/l. On gel filtration we found that the lambda and kappa chains were eluted corresponding to intact free light chains with molecular weights of about 22,000 and 44,000. Fragments of light chains were detected in only one patient (no. 4). In the deposits however intact light

## DISCUSSION

In this study we have demonstrated elevated concentrations of lambda light chains in two of four



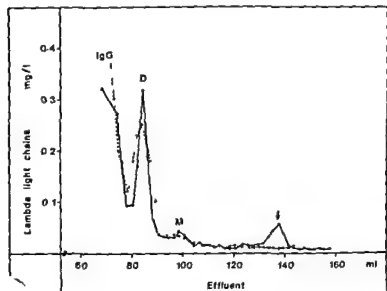
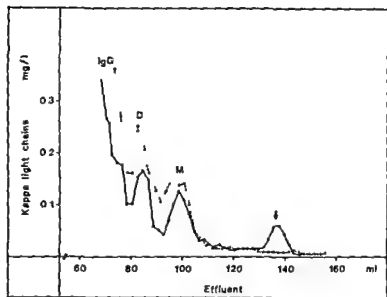


Fig 2 Measurements of kappa and lambda light chains after gel filtration on Sepharose 6B in a patient with localized amyloidosis. The arrow shows an elevated peak of light chain fragments.

as well as fragments of light chains have been demonstrated (14).

In patients with localized amyloidosis the mean D/M ratio of kappa chains was 1.6 compared to 1.2 in normal sera. For lambda it was 3.9 compared to 2.7 in normal sera. The values are not significantly different from normal, probably due to the small number of patients. Two patients (nos. 2 and 3) however had increased D/M ratios of both kappa and lambda chains. This is suggestive of an increased polymerization rate in localized amyloidosis (Fig. 1). The amount of tetrameric lambda light chains was accentuated in patients with localized amyloidosis but precise quantitation

was not possible due to contamination of immunoglobulins. The ratio kappa/lambda chain was 0.87, i.e. a relatively higher increase in lambda than in kappa chain concentration. This is the opposite of normal sera (10) but the difference is not significant, probably due to the small number of patients. Elevated polymerization rate and elevated concentration of lambda chains may explain why lambda chains are most often encountered in amyloid deposits (4).

An abnormal polymer of kappa chains has been demonstrated in another patient (13). Interestingly, this patient had nodular glomerulosclerosis and deposits of kappa chains detected by immunofluorescence.

nce Staining reactions for amyloid were  
Thus deposition of light chains does not  
lead to amyloidosis

ients with secondary amyloidosis the mean  
f both kappa and lambda chains were ele  
this is correlated to impairment of renal

We have previously demonstrated an in  
relation between the concentration of free  
ams and the glomerular filtration rate (11)  
centration of light chains and the D/M ratio  
ffer significantly from the values observed  
its with similar renal insufficiency of other

Thus elevated concentrations of light  
e not per se lead to amyloid deposits

of 11 patients with rheumatoid arthritis had  
values of light chains without any sign of  
osis The significance of these findings is

own A similar frequency of elevated light  
a rheumatoid arthritis (2 of 40 patients) has  
cribed by Epstein and Tan (2) All patients  
erculosis had normal values for light

Thus prolonged stimulation of the immune  
does not necessarily lead to increased light  
oncentration This is in agreement with the  
t that secondary amyloid proteins have a  
component of non immunoglobulin origin

## ACKNOWLEDGEMENT

ly was supported by grants from the Danish Medi  
cine Council

## REFERENCES

1. E. P. Enksen N. Hermodson M. A. &  
son L. H. The major proteins of human and  
key amyloid substance Common properties in

cluding unusual N Terminal amino acid sequences  
FEBS Lett 19 (2) 169 1971

2. Epstein W. V. & Tan M. Increase of L-chain proteins in the sera of patients with systemic lupus erythematosus and the synovial fluids of patients with peripheral rheumatoid arthritis Arthritis Rheum 9 (5) 713 1966
3. Eriksen H. E. A case of primary localized amyloidosis in both tonsils J Laryngol Otol 84 525 1970
4. Glenner G. G. & Page D. L. Amyloid amyloidosis and amyloidogenesis Int Rev Exp Pathol 15 1 1976
5. Glenner G. G. Terry W. Herada M. Iersky C. & Page D. Amyloid fibril proteins. Proof of homology with immunoglobulin light chains by sequence analyses Science 172 1150 1971
6. Jeppesen F. & Schaldemose H. J. Primary amyloid tumor of trachea Ugeskr Læger 132/38 1771 1970
7. Kyle R. A. & Bayrd E. D. Amyloidosis Review of 236 cases Medicine (Baltimore) 54 (4) 271 1975
8. Rosenthal C. J. & Franklin E. C. Variation with age and disease of an amyloid A protein related serum component J Clin Invest 55 746 1975
9. Skinner M. Benson M. D. & Cohen A. S. Amyloid fibril protein related to immunoglobulin lambda chains J Immunol 114 (4) 1433 1975
10. Söling K. Free light chains of immunoglobulins in normal serum and urine determined by radioimmunoassay Scand J Clin Lab Invest 35 407 1975
11. Söling K. Polymeric forms of free light chains in serum from normal individuals and from patients with renal diseases Scand J Clin Lab Invest 36 447 1976
12. Söling K. Normal values for free light chains in serum in different age groups Scand J Clin Lab Invest 37 21 1977
13. Söling K. Söling J. Jacobsen N. O. & Thomsen O. F. Nonsecretory myeloma associated with nodular glomerulosclerosis Acta Med Scand To be published
14. Terry W. D. Page D. L. Kimura S. Isobe T. Osseman E. F. & Glenner G. G. Structural identity of Bence Jones and amyloid fibril proteins in a patient with plasma cell dyscrasia and amyloidosis J Clin Invest 52 1276 1973
15. Waldenström J. G. Amyloid Acta Med Scand 199 145 1976



## Prognosis in Hypertrophic Obstructive Cardiomyopathy

Erik Orinius

*From the Division of Cardiology, Department of Medicine Thoracic Clinics  
Karolinska Hospital Stockholm Sweden*

ACT Thirty-eight non-operated patients with hypertrophic obstructive cardiomyopathy (HOCM) were followed for 1-18 years (mean 8). Thirty patients died, nine of them instantaneously and no other apparent cause of death. The findings on the first admission did not discriminate between those who died and those who survived during the observation period nor did the findings at catheterization at rest or left ventricular angiography. However, cardiac enlargement on chest X-ray was significantly more common in the deceased group: 75% against 27%, as was the absence of a q-wave in lead III on the first ECG: 83% against 42%. The combination of complete Q in lead III and cardiac enlargement on chest X-ray at the initial examination was present in 11 of the deceased (75%) and in only 3 of 24 survivors (13%). This can be used to select patients for prophylaxis against ventricular fibrillation according to the literature, is the main mechanism of instantaneous death in HOCM.

*Key words:* hypertrophic obstructive cardiomyopathy.

Acta Med Scand 206 289-292 1979

Mortality in hypertrophic obstructive cardiomyopathy (HOCM) is high: the estimated ten year figure is 35% (7). Most deaths are sudden (7) and more due to arrhythmias than to obstruction (6). An ECG was recorded immediately after a semi-erect HOCM patient: ventricular fibrillation (VF) was found in all (11). Twenty-four hour ambulatory ECG monitoring revealed paroxysmal ventricular tachycardia in 16 of 70 HOCM patients. Nine of these 16 patients died suddenly during the next two months (14). Otherwise sudden death is to have been unpredictable in HOCM. Before the main purpose of this follow-up study of non-operated HOCM patients was to find predictors of death and especially of instantaneous

## PATIENTS AND METHODS

In 1960-77 HOCM was diagnosed here in 40 patients who were not treated surgically. Two of the patients could not be traced at a follow-up study in 1978. Of the remaining 38 patients, 26 were males and 12 females, aged 13-65 years (mean 38) when first seen here.

The patients were examined by left and right heart catheterization and left and/or right angiocardiology. The diagnosis of HOCM was based on a left and/or right ventricular outflow tract gradient at rest of  $>5$  mmHg either spontaneously or following a premature beat or by isoprenaline provocation and/or angiocardiology evidence of encroachment of the ventricular cavities by the interventricular septum or in the left ventricle the anterior leaflet of the mitral valve.

## RESULTS

During the 1-18 years (mean 8) that the 38 patients were followed, 12 (32%) died. The estimated mortality was 22% at five years and 58% at ten years.

In ten of the deceased patients HOCM seemed to have been the main cause of death. The cause of death was obscure in the other two, one of whom developed frank pulmonary edema and hypotension during gastrointestinal bleeding and blood transfusion and the other died instantaneously and the autopsy disclosed advanced coronary arteriosclerosis. In one of the ten patients who died from HOCM the cause of death was cerebral emboli. Three of the remaining nine developed increasing symptoms of heart failure on effort before death but died instantaneously. In the other six patients the death was unexpected and instantaneous. Thus, totally nine patients without cardiac symptoms at rest died instantaneously without any other known cause than HOCM. Two of the latter patients were on  $\beta$ -blocking drugs compared with seven of the 26 survivors ( $p > 0.05$ ).

*Abbreviations:* HOCM = hypertrophic obstructive cardiomyopathy; VF = ventricular fibrillation; PWC = pulmonary capillary wedge pressure.

**Table 1** Symptoms ECG patterns and findings at left ventricular angiography on first admission in 26 survivors and 12 non survivors

None of the differences between deceased and survivors is significant ( $p > 0.05$ )

	Deceased (%)	Survivors (%)
<i>Symptoms</i>		
Dyspnea	67	38
Chest pain	50	38
Palpitations	33	19
Syncope	8	23
<i>ECG pattern*</i>		
Delta waves	8	0
Abnormal Q waves	42	25
Left ventricular hypertrophy	50	50
<i>Left ventricular angiography</i>		
Encroachment of the left ventricular cavity by the interventricular septum and/or the anterior mitral leaflet	90	64
Mitral incompetence	40	24

\* Criteria: delta waves  $\geq 0.03$  sec; abnormal Q waves  $\geq 0.04$  sec; LVH R in V5/CR5  $> 27$  mm or R in V5/CR5 + S in V1/CR1  $> 35$  mm and ST-T depression in V5/CR5

Besides the 12 deaths during the observation period one patient was resuscitated from VF. Two other patients developed syncope and second or third degree AV block. Although asystole was not recorded it is the most probable cause of their syncope. The initial ECG in one of these two patients showed left anterior hemiblock plus right bundle branch block. The other patient had no conduction defect when first seen but had a left bundle branch block when admitted for syncope. Both these patients received pacemakers and another two were being paced when first seen. Only two of these four patients could be paced from the atria. Both are alive, as is one of the two with ventricular pacemakers.

The incidence of proven HOCM in first degree relatives as well as suspected HOCM (sudden death or heart disease at early age) was 22%. There was no difference in the familial incidence between non survivors and survivors (both 44%).

Some of the symptoms on the initial admission are shown in Table 1. The cause of palpitations was atrial fibrillation in all with documented arrhythmia.

All the 38 patients had a systolic murmur of mitral regurgitation type when first seen. Delayed onset (as measured on phonocardiogram from fourth left costal space in the 100 Hz channel) occurred about 60% of both those who survived and those who did not.

Heart volume on the initial chest X-ray in erect position (8/12) was increased significantly more often among the deceased (75%) than among the survivors (36%) ( $p < 0.01$ ).

Some ECG patterns commonly described in HOCM are presented in Table 1 as they occurred at the first recording. Two patients had paced hearts and the ECG could be evaluated in only 36 patients.

When the first ECG of the deceased and survivors were compared, the deceased were more often found to lack a q wave of any amplitude in lead II (10 of 12 against 11 of 36) ( $p < 0.05$ ). The two deceased with a q in III had only two among the dead patients with a rS configuration in aVL while this QRS pattern occurred in only one of the 14 survivors with a q in III ( $p < 0.05$ ).

There was no significant difference between patients with and without a q in III with regard to QRS axis, occurrence of fascicle/bundle branch blocks, left ventricular hypertrophy or abnormal waves in precordial leads. The three patients with rSr in aVL (and q in III) were all aged 17 years, all the other three patients below age 22 had a q in III. These three patients with rSr in aVL had to have a more vertical mean QRS axis than the remaining 31 patients but the difference was not significant (80° against 15°;  $p > 0.05$ ).

The only association with the lack of a q in III was an increased heart volume at chest X-ray (15 against 8 of 21;  $p < 0.05$ ). rSr in aVL was seen together with normal heart volume in 15 patients, combination of no q in III and increased heart volume was present in 9 deceased and 3 survivors while rSr in aVL and normal heart volume was found in 2 deceased and 1 survivor. This series combining these two criteria would have correctly predicted 11 of 12 deaths and 4 of 24 survivors. All the 12 instantaneous deaths from HOCM were among the predictable deaths. Four of these 12 deaths occurred within one year, six within three and all within 12 years. The two patients who developed a Stokes-Adams attack during the observation period were not among the four with wrongly predictable

Findings at the heart catheterization on admission  
the differences between deceased and survivors  
( $p > 0.05$ )

	Deceased (%)	Survivors (%)
supine		
cardiac output (relative to regression line -)	17	8
arterial outflow tract (>5 mmHg) spontaneously		
arrhythm	75	46
ectopic beat and/or supraventricular end pressure (>13 mmHg)	85	54
arterial outflow tract (>5 mmHg) spontaneously		
arrhythm	17	27
ectopic beat and/or supraventricular end pressure (>13 mmHg)	17	31
right ventricular end pressure (>8 mmHg)	92	77
left ventricular end pressure (>8 mmHg)	58	54
cycle exercise supine		
cardiac output (relative to regression line -)	50	50
PWP		
cardiac regression line D (%)	100	95

left ventricular angiography on the admission did not show any significant difference between the deceased and the survivors (Table II)

heart catheterization on the first admission a tendency for more severe results in the deceased group but there were no significant differences at rest (Table II)

of the patients had a left and/or right outflow tract gradient at rest spontaneously or on provocation the left ventricular gradient was significantly higher among patients with radiologically increased heart volume (in the erect position) than in patients with normal heart volume (40 against 14 mmHg)

pulmonary capillary wedge pressure (PWC) related in relation to cardiac output in Fig. 1 the PWC value among the deceased during

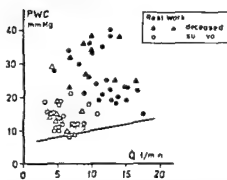


Fig. 1 PWC in relation to cardiac output ( $\dot{Q}$ ) in supine position at rest and during bicycle exercise — = Regression line in normal individuals - - - = +2 SD (2)

exercise was 23 mmHg, only 55% of the survivors reached this figure ( $p < 0.05$ ). Only one of the four patients with wrongly predictable death fell below that borderline.

## DISCUSSION

Although this series differs from other series in that it does not include any children or any patients treated surgically the annual mortality 4% is rather similar to the 3.5–6.6% in four other studies (1, 5, 7, 10). The proportion of sudden deaths is also similar in these five series 50–63% (1, 5, 7, 9).

In this series no difference was found in outflow tract gradient of the left ventricle at rest between deceased and survivors, nor in left ventricular end diastolic pressure at rest, as was similarly reported by (9). It has been suggested that the left ventricular outflow tract gradient may decrease with age (7). That was not the case in this series. The gradient was 20 mmHg in patients below 40 years and 32 mmHg above ( $p > 0.05$ ). Although the heart volume in the erect position also tended to increase with age (454 ml/m<sup>2</sup> BSA below 40 years and 515 ml/m<sup>2</sup> above,  $p > 0.05$ ) patients with enlarged hearts had significantly greater outflow tract gradients in the left ventricle (400 mmHg against 14 mmHg,  $p < 0.01$ ). Frank and Braunwald (5) also found greater gradients in patients with moderate or marked enlargement compared to patients with normal or slightly enlarged hearts. The cardiac enlargement may be caused to some extent by left ventricular hypertrophy but in the two cases with the outstanding enlargement (both 800 ml/m<sup>2</sup> BSA) the left ventricular outflow tract gradients were also rather

high 60 and 44 mmHg. These large heart volumes corresponded to dilated left ventricles on the angiogram and both patients had symptoms of heart failure. These findings do not support the view that the gradient decreases as the myocardium fails.

Frank and Braunwald (5) found slight cardiac enlargement on chest X-ray in 29% and moderate or marked enlargement in 41% making a total of 70% of their patients compared to 42% in the present series. The heart volume (in the prone position) is also increased in relation to total hemoglobin in HOCM (3). The prognostic value of that relation has been noted in a small series (13) but in the present material the heart volume did not discriminate better when related to total hemoglobin.

The frequent lack of a q of any size in lead III in the deceased group might have several explanations. A different position or configuration of the heart as measured by the mean QRS axis was not the cause nor were intraventricular conduction disturbances. As the hearts were often radiologically enlarged a generalized hypertrophy and/or dilatation may contribute to the absence of a q in III although the left ventricular hypertrophy pattern in the ECG was not present to a significant degree. An abnormal septal anatomy/activation is another possible explanation but positive support is lacking.

The figures behind the predictive value of rSr in aVL are so small that although statistically significant no conclusion ought to be drawn from them. However rSr may be the equivalent in young patients with small vertical hearts to the lack of q in III in patients with enlarged and more horizontal hearts.

As VF seems to be the main mechanism of instantaneous death in HOCM patients the consequence of finding a high risk of such death might be to give the patient long term drug prophylaxis against VF. A serious side effect of antiarrhythmic drugs is a prolonged asystole if complete AV block supervenes. In this series however neither of the two patients developing high degree AV block and Adams Stokes attacks had the findings predictive of instantaneous death.

## CONCLUSION

At the first examination in HOCM patients the combination of a complete lack of a q wave in lead

III and any degree of cardiac enlargement on chest X-ray indicates a high risk of instantaneous death during the next few years.

## REFERENCES

- Adelman A G, Wagle E D, Ranganathan G D, Kidd B S L, Bgelow S, Silver M D. The clinical course in mitral regurgitation and aortic stenosis. *Ann Intern Med* 77: 515 1972.
- Altman L & Dittmer D S. Respiratory physiology. *Federation of Societies for Experimental Medicine* p 397. Bethesda Maryland 1971.
- Bevegård S, Jonsson B & Karlfil. Left ventricular aortic and pulmonary stenosis: asymmetrical hypertrophy and derangement of the bundles of the ventricular wall. *Acta Med Scand* 172: 769 1963.
- Ekelund L G & Holmgren A. Hemodynamics during exercise. *Circ Res* 1: 38 1967.
- Frank S & Braunwald E. Idiopathic subaortic stenosis. Clinical analysis of 16 with emphasis on the natural history. *Circ* 37: 759 1968.
- Goodwin J F & Kirkler D M. Arrhythmias and cause of sudden death in hypertrophic cardiomyopathy. *Lancet* 937 1976.
- Hardarson T, de la Calzada C S, Cennaro Goodwin J F. Prognosis and mechanism of hypertrophic obstructive cardiomyopathy. *Am J Med* 2: 1467 1973.
- Jonsell S. A method for the determination of heart size by teleroentgenography (a heart index). *Acta Rad* 10: 375 1939.
- Krethaus W, Kuhn H & Loogen F. A. Deaths in the course of hypertrophic obstructive cardiomyopathy. In: *Cardiomyopathy and arrhythmias* (ed. M. Kaltenbach, F. Loogen & A. Olsen) p 300. Springer Verlag Berlin 1978.
- Loogen F, Kuhn H & Krethaus W. The history of hypertrophic obstructive cardiomyopathy and the effect of therapy. In: *Cardiomyopathy and arrhythmias* (ed. M. Kaltenbach, F. Loogen & A. Olsen) p 286. Springer Verlag Berlin 1978.
- Maron B J, Roberts W C, Edwards J E, Lister H A, Foley D D & Epstein S E. Sudden death in patients with hypertrophic cardiomyopathy. Characterization of 76 patients with histopathological findings. *Am J Cardiol* 41: 803 1978.
- Maurea Nylén G & Sollberger A. Ventricular volume. *Acta Card* 10: 336 1975.
- Orinius E & Pernow B. Primary cardiomyopathy. *Acta Med Scand* 197: 45 1974.
- Savage D D, Sedes S F, Maron B J & Epstein S E. 24 hour ambulatory electrocardiographic monitoring of patients with obstructive hypertrophic cardiomyopathy. *Circ* (Suppl) 111: 716 1977.

# Myocardial Infarction in Malmö during the 10 Year Period 1963-1972

Sven Olof Isacson and Bengt W. Johansson

From the Section Department of Internal Medicine, Malmö General Hospital, Malmö, Sweden

ACT Myocardial infarctions in Malmö during the 10-year period 1963-72 have been studied. Data from myocardial infarction decreased both among men during this period but not among women. The incidence of hospital treated increased significantly among men mainly because of an increase in primary infarctions. The one-year mortality in this hospital material did not increase during the period. The number of days of sick leave during 12 months before primary infarction was significantly higher than expected. The number of sick leave during the year after primary infarction remained unchanged throughout the period. The mortality figures relate to all age groups. Among 2111 men and 1409 women. The hospital mortality relates to men and women aged 65 years or over and comprises 1323 men and 279 women during the period concerned. The reduced mortality and incidence of hospital treated infarction are mainly explained by the fact that more men seek treatment leading to a better prognosis. The duration of sick leave after infarction is probably due to causes other than strictly medical factors.

Key words: myocardial infarction, morbidity, mortality.  
Acta Med Scand 706 793 1979.

On the prognosis after myocardial infarction mainly dealt with the annual mortality (1, 3, 6, 19, 73, 9) and the patients' ability to return to work (13, 7, 74, 75). The patients' state of health 6 years after myocardial infarction has also been studied (7). We have endeavoured to elucidate certain other aspects of myocardial infarction and have studied short-term trends in several variables over a 10-year period in a defined population. The variables studied are mortality from infarction in the total population, incidence of hospital treated infarction and survival in the hospital treated patients and

sick leave during the year before and after onset of infarction.

## PATIENTS AND METHODS

The study comprises 1323 men and 279 women aged 65 years or below who were admitted to the Department of Medicine, Malmö General Hospital during the period Jan 1, 1963-Dec 31, 1972. This is the only hospital for treatment of acute cases in the city and with few exceptions all patients with acute myocardial infarction in Malmö are treated in our department. Of the 1323 men 1861 are presented as primary infarctions, 189 had two infarctions and 57 three or more. Sixteen men evenly distributed over the 10-year period were excluded owing to incomplete data. Of the 279 women 217 had primary infarctions, 43 had two infarctions and 6 three or more. These women were excluded owing to incomplete information. The results are mainly restricted to individuals aged 64 years or below and therefore focus is on patients with primary infarctions.

The diagnosis of infarction has been based on rises in transaminase, ECG abnormalities and chest pain (9). Information on number of days of sickness benefit and disability pensions has been obtained from the National Insurance Office. The sickness index, i.e. the number of days of sickness benefit entitlement per person per year has been calculated for each individual in the same way as in the statistics regularly issued by the National Insurance Office. Patients who have retired or moved out of the district have been excluded from the calculations of the sickness index.

The date of death of those who have died has been determined in order to calculate survival after infarction. The total mortality from myocardial infarction in the City of Malmö which has been calculated for all ages is based on the ICD code for myocardial infarction according to the death certificates as calculated by the Swedish Central Bureau of Statistics which scrutinizes all death certificates issued in Sweden. Information about the incidence of post mortem examinations in the city has been obtained from the Department of Pathology, Malmö General Hospital.

Age-specific prevalences have been calculated per 100 000 inhabitants for each age group. The statistical calculations have mainly comprised tests for trend in contingency tables which permit assessment of any significant changes, increases or decreases during the 10-year period.



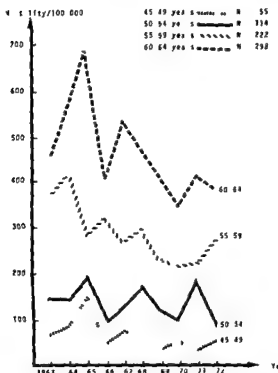


Fig 1 Number of deaths from myocardial infarction per 100 000 45-64-year-old men in the City of Malmö in 1963-72

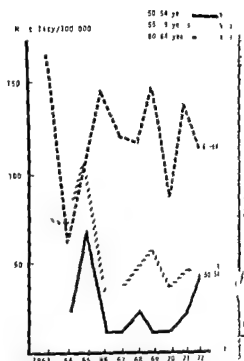


Fig 2 Number of deaths from myocardial infarction per 100 000 50-64 year-old women in the City of Malmö in 1963-72

## RESULTS

### Mortality from myocardial infarction

The total mortality from myocardial infarction based on death certificates for men aged 45-64 years is shown in Fig 1 and for women aged 50-64 years in Fig 2. A significant reduction in mortality ( $p < 0.05$ ) was found among men in the age

groups 35-39, 45-49, 55-59 and 60-64. At ages 40 and above the reduction is somewhat more pronounced ( $p < 0.01$ ). No corresponding change can be demonstrated among women during the period.

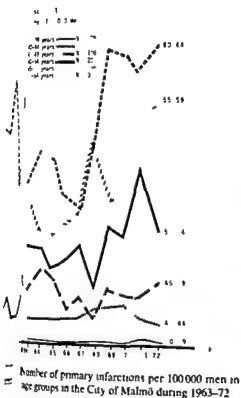
During the 10-year period 2111 deaths from myocardial infarction were recorded among men and 1409 among women living in the City of Malmö. 35% of the men and only 13% of the women died before the age of 65 years. The mode of autopsies on which the death certificates were based remained constant at about 90% throughout the period at the ages concerned.

Table 1 Total number of myocardial infarctions and proportion of primary infarctions by age and sex during the 10 year period

	Women	Men
Total no of infarctions	279	1323
Of which primary infarctions in the age groups		
0-39	2	28
40-44	5	55
45-49	9	106
50-54	24	202
55-59	61	296
60-64	101	317
65	14	37
	(77.8%)	(80.2%)

### Incidence of hospital treated infarction

The total number of infarctions during the 10-year period and the proportion of primary infarctions in each age group are shown in Table 1. The change in incidence of infarction during the 10-year period in the various age groups for men up to 65 years is completely explained by the increase in primary infarctions shown in Fig 3. No increase in the incidence of two or more infarctions during the period could be demonstrated. A significant increase in primary infarctions was found for men in the age groups 0-39 ( $p < 0.01$ ), 50-54 ( $p < 0.05$ ), and



01) and 60-64 ( $p < 0.01$ ). For women there is a consistent pattern: the number of primary infarctions in the different years is relatively small. When age groups 0-39 and 40-44 years are pooled, a slight increase ( $p < 0.05$ ) did occur during the period, but the total number of infarctions in these age groups was only seven.

#### Survival among 45-64 year old men with myocardial infarction treated in hospital

One-year mortality including hospital mortality and mortality after discharge, calculated from the date of admission to hospital, is shown as the one year survival in Fig. 4. The figures relate to the two age classes of men 45-54 and 55-64. No significant change during the period could be demonstrated. There is no trend towards an increased proportion of survivors; the curves are almost identical for the two age groups, with 67% still alive after one year. There is some drop in survival due to patients moving out of the district during the period, but the figures are constant throughout the period: only about 0-3 individuals per year in the various age groups ( $N = 786/22$  trials).

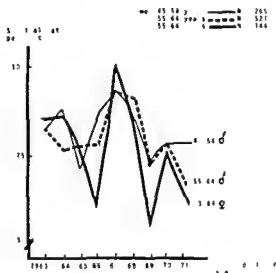


Fig. 4. Proportion of men and women still alive 1 year after first admission to hospital for myocardial infarction in the City of Malmö 1963-71.

#### Sick leave during the year before the first infarction

Figs. 5 and 6 show the morbidity expressed as the observed number of days of sick leave during 12 months before the first infarction. The figures are compared with the expected number of days of sick leave, i.e. the mean value for the age groups for the whole city. The figures relate to the age group 50-59, where the excess morbidity was highest, with a sickness index 1.8 times higher than expected in men (46 days compared to 26 days).

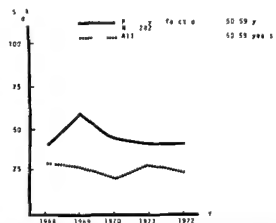


Fig. 5. Number of days of sick leave during 12 months (sickness index) before infarction in men with primary infarctions compared to all men of the same age in the City of Malmö 1968-72.

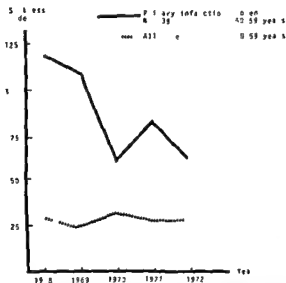


Fig 6 Number of days of sick leave during 12 months (sickness index) before infarction in women with primary infarction compared to all women of the same age in the City of Malmö 1968-72

expected sick leave) and 3 times higher than expected in women (86 days compared to 29)

#### *Sick-leave during the year after primary infarction*

In order to obtain at least a rough measure of the burden on the community caused by myocardial infarction over a period the average number of days of sick leave per individual during 12 months after primary infarction has been calculated for individuals who were still alive at the end of one year and had not moved from the city or retired. Fig 7 shows the figures for men in the age groups 45-54 (out of 215 included 6 moved or retired) and 55-64 (362 out of 408 survivals included 46 moved or retired). It is obvious that the infarction patients as a group did not change during the period. The age difference of 10 years between the groups seems to have had a negligible influence on the number of days of sick leave.

### DISCUSSION

Myocardial infarctions in Malmö have previously been analysed in various contexts (2, 3, 9, 10, 21).

The reduced mortality from infarction during the period studied in this investigation may be due to various causes. Altered classification is one possibility. The cause of death is based on death certi-

icates. The incidence of autopsies in Malmö, however, very high, about 90% throughout the period in the relevant ages. It is therefore unlikely that altered classification contributed to the reduction. A reduced incidence of infarction or a changed mortality would also explain the findings. A reduced incidence of fatal infarction with a change in the total incidence of infarction is a possible explanation. Such a change might be due, for example, to changes in the risk factors. The fact that the reduction only involves mortality suggests, however, that the change is not explained by altered classification but is due to a true decrease in mortality from infarction caused by factors other than cohort effects. A reduction in mortality from infarction has also been found in other countries in recent years, particularly in the USA. An increase in the incidence of hospital-treated myocardial infarction has previously been reported from Malmö for the period 1935-68 (2, 9). The authors were of the opinion that the increase cannot be explained by altered diagnostic criteria alone, or by an increase in the incidence among patients with myocardial infarction seeking hospital treatment, but is due to a true increase in incidence. Our study population shows a similar trend. If the increase in incidence is considered an isolated phenomenon, a true increase in the population, altered diagnostic criteria and

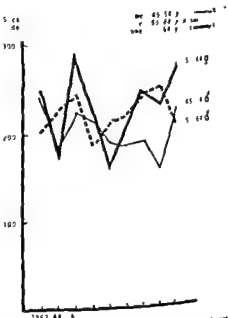


Fig 7 Number of days of sick leave (sickness index) during the first 12 months after primary infarction for men and women in the City of Malmö 1961-71

among patients with chest pain to seek treatment are all factors which separately might contribute to the increase in treated myocardial infarctions. The one year survival in the hospital treated patients was not changed significantly during 9 of the 10 years studied. The one year survival during the year after discharge from hospital has been reported in several publications (1, 3, 8, 11, 19, 23) as the mortality during hospital stay (14, 15). In a study from Gothenburg, Sweden (23) found that 87% of men and women with primary infarction were alive one year after onset. The 13% had died. Reinfarction in the hospital treated patients increased the mortality to 37% during the first year after discharge. In a cooperative CCU study (7) the total mortality was 10% at the age of 39 and increased to 20% at the ages of 60-69 years. In Malmö was established in 1968 in the year of the period covered by this study. The results among our study population during the 10-year period is essentially the same as in other Swedish studies. We found no trend towards increased mortality during the 10-year period. The individual observations thus does not seem to have decreased during this study period in this hospital material. Our observations show that there has been a significant reduction in mortality from infarction during the 10-year period at the same time as the incidence of hospital treated myocardial infarction has risen significantly mainly due to an increase in primary infarctions. The one year survival has not changed. If the incidence of myocardial infarction was in reality unchanged during the 10-year period the most likely explanation of our findings would be that an increased number of patients had been treated in hospital because of myocardial infarction and that the mortality is lower among those treated than among those not treated in hospital. This explanation seems reasonable. To our knowledge hospital treatment of myocardial infarction is definitely superior to other forms of treatment. The influence of treatment in the CCU has been assessed in this material. We should also note that in practice patients with diagnosed myocardial infarction are not treated in their homes. It is known that myocardial infarction is preceded by a period of increased morbidity (1) and Lundman (7) found a history of angina in 45-60% of patients with myocardial infarction mainly primary aged below 69 years (7).

Hypertension and diabetes were also more prevalent than expected. The same authors also demonstrated a significantly higher prevalence of hypertension and diabetes as well as of angina pectoris in the histories of women than of men. We found a definite increase particularly among women in the number of days of sick leave during 12 months before primary infarction. This observation is naturally an expression of an increased morbidity probably angina pectoris, hypertension and diabetes as contributory factors although other causes are also possible.

Rehabilitation after myocardial infarction has attracted much interest in recent years (5, 12, 17, 18, 20). The main reason is the possibility of promoting the patient's return to work. The time between onset of infarction and return to work differs however enormously between studies from different countries. Only 17% of men with infarction aged 67 and below in a Swedish study (27) were working after 3 months, 63% after 12 months and 70% after 24 months. In a Danish study (13) 80% of surviving patients had resumed work within 3 months after discharge from hospital. In a study from Norway (22) only 40% of men had returned to work at the time of follow up 2-4 years after discharge. A major factor in that study was the extremely low proportion 9% of poorly educated men from rural areas who had returned to work. Similar findings are reported in a study from Finland (24). All these studies are from the Nordic countries and are fairly comparable with respect to age.

The tendency to resume work evidently depends on a number of circumstances including socio-economic factors. Differences between countries are probably due to differences in health insurance systems rather than differences in rehabilitation. It is therefore difficult to compare the burden on the community caused by myocardial infarction in different countries. During a period of relative stability on the labour market and only minor changes in health insurance benefits more intensive rehabilitation should influence the duration of sick leave after infarction. This was not so in our material. As a group patients with myocardial infarction were sick listed to the same extent at the beginning and end of the period. The greatly increased interest in active treatment during the acute phase of infarction during the 1960s is thus not reflected by more active occupational rehabilitation.

tion To judge from the studies of Kjoller (13) and Weinblatt et al (25) most infarction patients seem to be able to resume work within 3 months In the City of Malmö the duration of sick leave remained long throughout the 10-year period studied Medical factors are probably of minor importance for the long duration of sick leave

## REFERENCES

- 1 Badger G F & Liebow I M Myocardial infarction in the practices of a group of private physicians IV Factors related to the longevity of patients with myocardial infarction during the first five years *J Chronic Dis* 21 473 1968
- 2 Björck G Blomqvist G & Sievers J Studies on myocardial infarction in Malmö 1935 to 1954 I Morbidity and mortality in a hospital material *Acta Med Scand* 159 253 1957
- 3 Björck G Sievers J & Blomqvist G Studies on myocardial infarctions in Malmö 1935 to 1954 III Follow up studies from a hospital material *Acta Med Scand* 162 81 1958
- 4 Björck G & Wedelin E M The return to work of patients with myocardial infarction *Acta Med Scand* 175 215 1964
- 5 Helander E Economic aspects of the rehabilitation of patients with cardiovascular and cerebrovascular diseases *Acta Cardiol (Suppl)* 14 53 1970
- 6 Helmers C Short and long term prognostic indices in acute myocardial infarction *Acta Med Scand (Suppl)* 555 1974
- 7 Henning R & Lundman T Swedish co-operative CCU study A study of 2008 patients with acute myocardial infarction from twelve Swedish hospitals with coronary care unit Part I A description of the early stage *Acta Med Scand (Suppl)* 586 1975
- 8 Hofvendahl S Influence of treatment in a coronary care unit on prognosis in acute myocardial infarction A controlled study in 271 cases *Acta Med Scand (Suppl)* 519 1971
- 9 Johansson B W Myocardial infarction in Malmö 1960-1968 *Acta Med Scand* 191 505 1972
- 10 Johansson B W & Persson B Coronary heart disease in Malmö Incidence and long term follow up of the Kockum study In Skandia International Symposia Early phases of coronary heart disease pp 314-322 Nordiska Bokhandelns Forlag Stockholm 1973
- 11 Kannel W B McNamara P M Feinleib M & Dawber T R The unrecognized myocardial infarction Fourteen year follow up experience in the Framingham study *Geriatrics* 25 75 1970
- 12 Kellerman J J Modan B Levy M Feldman S & Kanv J Return to work after myocardial infarction Comparative study of rehabilitated and non rehabilitated patients *Geriatrics* 25 151 1968
- 13 Kjoller E Resumption of work after myocardial infarction *Acta Med Scand* 199 379 1971
- 14 Meltzer L E & Kitchell I R The design and current status of coronary care In Textbook of coronary care (ed L E Meltzer & A I Olsson) pp 3-25 Excerpta Medica Amsterdam 1971
- 15 Norris R M Brandt P W T Caughey D A J & Scott P J A new coronary prognosis *Lancet* i 274 1969
- 16 Peel A A F Semple T Wang I Lanza M & Dall J L G A coronary prognosis scale grading the severity of infarction *Br Heart J* 1962
- 17 Report of a joint Working Party of the Royal College of Physicians of London and the British Society on Rehabilitation after Cardiac Disease Cardiac rehabilitation 1975 *J R Coll Physicians Lond* 9 281 1975
- 18 Report of the Task Force on Cardiovascular Rehabilitation National Heart and Lung Institute Recommendations and opportunities for rehabilitating the coronary disease patient Publication (NIH) 75-001 Division of Health Education and Welfare Washington D C Dec 15 1974
- 19 Richards D W Bland E F & White P completed twenty-five year follow-up study of patients with myocardial infarction *J Clin Pathol* 4 415 1956
- 20 Sanne H Exercise tolerance and physical activity in non selected patients after myocardial infarction *Acta Med Scand (Suppl)* 551 1973
- 21 Sievers J Myocardial infarction Clinical course and outcome in three thousand thirty-six cases *Acta Med Scand (Suppl)* 406 1963
- 22 Sire S & Eldjarn K Arbeidsforberedelse efter hjerteinfarkt Efterundersøkelse av et nordnorsk materiale *Tidsskr Nor Lægeforen* 98 79 1974
- 23 Vedin A Wilhelmsson C Elmfeldt D Söderbergh J Tibblin G & Wilhelmsson L and non fatal reinfarctions during two years up after myocardial infarction *Acta Med Scand* 198 353 1975
- 24 Vuopala V Resumption of work after myocardial infarction in Northern Finland *Acta Med Scand (Suppl)* 530 1972
- 25 Weinblatt E Shapiro S Frank C & Seaman D Return to work status following first myocardial infarction *Am J Public Health* 56 169 1966
- 26 Wenger N Hellerstein H Blackwelder W C Castranova S Uncomplicated myocardial infarction *JAMA* 224 511 1973
- 27 Wilhelmsson C Vedin A Elmfeldt D Tibblin G & Wilhelmsson L Symptoms disability and treatment during two years after myocardial infarction *Scand J Rehabil Med* 8 85 1976
- 28 Woodhouse S P Subsequent mortality in surviving myocardial infarction *Br Med J* 1969

# Dobutamine in Left Heart Failure after Acute Myocardial Infarction

N Rehnqvist and T Lundman

From the Department of Medicine Serafimerlasarettet Stockholm Sweden

**ICT** Dobutamine a new positive ino-  
reg was given as i.v. infusion at a rate of  
2.5 µg/kg/min to nine male patients with a mod-  
erate left heart failure. The patients were  
in our CCU for acute myocardial infarction  
and had PEP/LVET above 0.40 on routine  
recording of systolic time intervals. PEP (prejec-  
tion phase) PEPI (PEP corrected for heart rate),  
left ventricular ejection time (LVET) and LVETI  
(LVET corrected for heart rate). Dobutamine in-  
creased contractility measured as shortening of PEP  
and also increased ejection fraction, meas-  
ured as PEP/LVET. Concomitantly heart rate in-  
creased significantly but no changes were noted in  
diastolic BP's. The positive inotropic effect  
of dobutamine was thus accompanied by a positive  
chronotropic effect which limits the usefulness of the  
drug in patients with recent AMI.

**Key words:** dobutamine, acute myocardial infarction, left  
heart failure, non-invasive parameters.

Acta Med Scand 206 299 1979

Due to a lack of clinically useful positive ino-  
tropic drugs Digitalis glucosides have their given  
therapy but there is a need for more potent  
drugs in general use include isoproterenol,  
noradrenaline and dopamine. Their use is  
limited with well recognized disadvantages:  
isoproterenol is chronotropic, arrhythmogenic,  
increases peripheral resistance. To overcome  
these disadvantages dobutamine was synthesized  
and shown in animal experiments to selectively  
increase myocardial contractility without inducing  
tachycardia or significant changes in  
mean aortic perfusion pressures (8).  
This study was performed to assess the effects of  
dobutamine on myocardial performance as meas-  
ured by systolic time intervals in patients with  
impaired cardiac function after recent acute  
myocardial infarction (AMI).

## PATIENTS AND METHODS

Nine men, mean age 58 years, treated in our CCU for AMI  
were investigated 5-17 (median 7) days after hospitaliza-  
tion for AMI. Patients who on routine recordings of  
systolic time intervals showed impaired cardiac function  
who were not on digitalis or  $\beta$  receptor blocking drugs and  
who received maximally 40 mg of furosemide (or a com-  
parable diuretic) were included in the study.

After 30 min rest an i.v. infusion of dobutamine was  
given using a constant rate infusion pump. The drug was  
diluted in 5% dextrose and given at a rate of 2.5, 5.0 and  
7.5 µg/kg/min during 30 min at each concentration. The  
systolic time intervals, heart rate and BP—measured by  
brachial artery catheterization—were registered twice  
during the pretreatment period, after 15 and 30 min on  
each dose and 15 and 30 min after the infusion.

The systolic time intervals were registered according to  
Weissler and Garrard (10) simultaneously with recordings  
of ECG, phonocardiogram and carotid pulse. The values  
registered were prejection phase (PEP) corrected for  
heart rate (PEPI), left ventricular ejection time (LVET)  
corrected for heart rate (LVETI) and PEP/LVET. Pa-  
tients with PEP/LVET above 0.40 were included in the  
study. Infusion was discontinued when no further im-  
provement in cardiac performance could be registered or  
if side-effects like severe palpitations, registered tachy-  
cardia or other severe arrhythmias supervened.

The paired *t* test was used to evaluate intrasubject  
changes in the registered parameters.

## RESULTS

One patient was investigated for only 15 min at 2.0  
µg/kg/min. The concentration and duration of infu-  
sion for the other patients were 5 µg/kg/min for 30  
min in three, 6 µg/kg/min for 30 min in one, 7.5  
µg/kg/min for 15 min in two and 7.5 µg/kg/min for  
30 min in two patients. The concentrations of 2.0  
and 6.0 µg/kg/min were due to a methodological

**Abbreviations:** AMI = acute myocardial infarction, CCU =  
coronary care unit, BP = blood pressure, PEP = pre-  
ejection phase, PEPI = PEP corrected for heart rate,  
LVET = left ventricular ejection time, LVETI = LVET  
corrected for heart rate, VEB = ventricular ectopic beat.

Table 1 Patient data and effect of different doses of dobutamine on PEP/LVET

Pat no	Age (y)	Days after AMI	Pre therapy	2.5 µg/kg/min		5 µg/kg/min		7.5 µg/kg/min		Posttherapy		Lev. (mmHg)
				15 min	30 min	15 min	30 min	15 min	30 min	15 min	30 min	
1	51	8	0.44	0.53	0.50	0.47	0.45	0.38	0.41	0.41	0.40	110
2	51	11	0.42	0.46	0.39	0.37	0.46	0.38	0.41	0.38	0.37	110
3	72	7	0.47	0.40 (2)	0.40 (2)	0.40	0.36 (4)	0.34	0.38 (6)	-	-	120
4	54	17	0.46	0.36	0.38	0.33	0.34	-	-	0.46	0.45	120
5	61	9	0.45	0.42 (2)	-	-	-	-	-	0.34	0.39	120
6	49	11	0.40	0.30	0.29	0.31	0.32	-	-	0.41	0.37	120
7	59	8	0.50	0.41	0.35	0.41	0.35	0.40	-	0.47	0.46	120
8	63	8	0.37	0.37	0.33	0.30	0.32	0.28	-	0.32	0.4	120
9	62	5	0.50	0.41	0.44	0.38	0.41	(0.25)	-	0.45	0.45	120
Mean	58	9	0.45	0.41	0.39	0.37	0.38	0.34	-	0.41	0.37	120

\* $p < 0.05$  \* \* $p < 0.001$ 

error PEP/LVET was reduced in all patients 12-28% (mean 23) suggesting improvement of myocardial function (Table 1). The change from pretreatment values is significant. The PEP/LVET had again increased significantly 15 min after infusion and no further increase was noted 30 min after infusion. Heart rate increased significantly during infusion but no changes were noted in systolic and diastolic BP (Figs 1 and 2).

The positive inotropic effect of dobutamine is also reflected by a significant shortening of PEP and PEPI (Fig. 3). No changes were noted in LVETI (Fig. 4). Three patients complained of palpitations during infusion. Four patients had ventricular ectopic beats (VEB) and two multiform ventricular beats during infusion. One patient developed a fall in BP from 140/85 to 100/60 mmHg. No other serious side-effects were noted. Blood laboratory tests were made before and after infusion and no changes were found in aminotransferases, electrolytes, serum creatinine or WBC.

### DISCUSSION

Patients with myocardial infarction complicated by severe left ventricular failure present a major

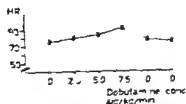


Fig. 1 Heart rate in relation to concentration of dobutamine infusion (mean ± S.D.). The increases at 5.0 and 7.5 µg/kg/min are significant.

therapeutic dilemma. Positive inotropic drugs like dopamine, noradrenaline, adrenaline and isoprenaline are all potentially dangerous, especially in the postinfarction phase because of their arrhythmogenic and energy-consuming effects. The lack of beneficial effect is also partly due to reflexes due to the initial actions. Isoprenaline has been shown to increase myocardial contractility after AMI but it also gives a marked chronotropic effect together with a decrease in peripheral resistance (2). Apart from these side-effects the drug is also arrhythmogenic. Dopamine even at high doses increases heart rate and peripheral resistance. Both these drugs are therefore very dangerous for the ischemic heart (4).

Dobutamine has been shown to exert a  $\beta_1$  adrenergic stimulation resulting in increased contractility with minimal positive chronotropic and vasoconstrictive effects. In AMI patients the drug has been shown to be

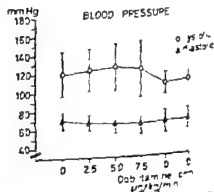


Fig. 2 Systolic and diastolic BP during different concentrations of dobutamine infusion (mean ± S.D.). No significant changes were noted.

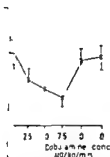


Fig. 3 Relation between PEPI and different concentrations of dobutamine. PEPI was significantly decreased by dobutamine.

output and decrease pulmonary arterial pressures without significantly changing left or systemic arterial BP (8). This effect has been claimed to be non-demanding in energy. In patients treated with dobutamine did not suffer infarcts than control patients. Further there was no increased frequency of pre-VEBs (3). Four of our nine patients showed an increase in ventricular ectopy during infusion. Increased frequency of VEB was concomitant with an increase in heart rate. An incidence of VEB is however not higher than expected in patients with recent AMI (6). As pointed out by Tenen et al. (9) the action of dobutamine is energy-demanding as in patients with severe AMI the shortening of PEPI is associated with an increase in heart rate and BP. In AMI patients with more severe signs of heart failure in the above study did not respond to pressure or PEPI but did show a significant increase in heart rate. These differences in response to dobutamine therapy depending on the disease remain unexplained. Compensatory mechanisms especially in patients with severe congestive heart failure may be relevant. In these patients the sympathetic drive is nearly maximal and further increase can be expected with a partly inotropic drug like dobutamine. In our patients had "subclinical left heart failure" accompanied with a decrease in PEP and PEPI as well as a lowering of PEP/LVET suggesting decreased contractility. PEP measured according to Kissler and Garrard (10) has been shown to correlate well with other parameters of contractility, preload and afterload—evaluated as pressure (5, 7). In our study afterload—evaluated as diastolic arterial pressures—did not

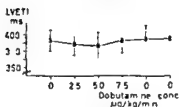


Fig. 4 LVETI in relation to different concentrations of dobutamine. LVETI was not changed by the drug.

change. Preload or left ventricular filling pressures are shown to remain unchanged or decrease with the drug. A decrease in preload is in itself associated with a prolongation of PEP (1). Accordingly there seems to have been an increase in contractility due to dobutamine. The other two systolic time intervals used were PEP/LVET which is correlated to ejection fraction (11) and LVET which parallels stroke volume (12). Measured by these parameters ejection fraction increased whereas stroke volume was unchanged. The increase in contractility is thus accompanied by the same decrease in diastolic as in systolic volumes. The clinical value of this observation is limited as the reduction in PEP or PEPI is accompanied by an increase in heart rate suggesting further increases in oxygen demand. This finding is discordant with original findings by Tuttle and Mills (8) in laboratory animals where the increase in contractility was not accompanied by increased heart rate. The present data from patients with mild left heart failure after AMI do not suggest that dobutamine in this situation has significant advantages over isoprenaline, dopamine or noradrenaline.

Patients in shock accompanying myocardial infarction also fail to improve with dobutamine infusions (9). However dobutamine may well be of value during a limited period in patients with forward failure due to other conditions than ischemia, i.e. septicemia, postvalvulotomy where a reversible myocardial damage supposedly is present. Results from the use of other  $\beta$  agonists are supporting this concept.

## REFERENCES

1. Beregovich J, Bianchi C, D'Angelo R, Diaz R & Rubler S. Haemodynamic effects of a new inotropic agent (dobutamine) in chronic cardiac failure. *Br Heart J* 37: 629, 1975.
2. Beregovich J, Reicher-Reiss H & Grishman A. Haemodynamic effects of isoprenaline in acute myocardial infarction. *Br Heart J* 34: 705, 1972.



- 3 Gillespie T A Ambos H D Sobel B E & Roberts R Effects of dobutamine in patients with acute myocardial infarction *Am J Cardiol* 39 588 1977
- 4 Holloway G A Jr & Frederickson E L Dobutamine a new beta agonist *Anesth Analg (Cleve)* 53 616 1974
- 5 Metzger C C Chough C B Kroetz F W & Leonard J J True isovolumic contraction time *Am J Cardiol* 25 434 1970
- 6 Rehnqvist N Ventricular arrhythmias prior to discharge after acute myocardial infarction *Eur J Cardiol* 4 63 1976
- 7 Talley R C Meyer J F & McNay J L Evaluation of the preejection period as an estimate of myocardial contractility in dogs *Am J Cardiol* 27 384 1971
- 8 Tuttle R R & Mills J Dobutamine Derivative of a new catecholamine to selectively increase contractility *Circ Res* 36 185 1975
- 9 Waagstein F Malek I & Hjalmarson A Use of dobutamine in myocardial infarction: reversal of the cardiodepressive effect of metoprolol *Clin Pharmacol* 5 515 1978
- 10 Weissler A M & Garrard C L Jr Systolic time intervals in cardiac disease I *Mod Cardiovasc Dis* 40 1 1971
- 11 — Systolic time intervals in cardiac disease *Concepts Cardiovasc Dis* 40 5 1971
- 12 Weissler A M Peeler R G & Rochill J Relationship between left ventricular ejection stroke volume and heart rate in normal subjects and patients with cardiovascular disease *A* 62 367 1961

## Atenolol Administered once Daily in Primary Hypertension

*Effects on Blood Pressure in Relation to Pre Treatment Plasma Renin Activity*Ove R Nilsson Bengt E Karlberg Olof Ohlsson  
Thomas Thulin and Kerstin Tolagen*From the Departments of Internal Medicine University Hospitals of Linköping  
Malmö and Lund Sweden*

CT The antihypertensive effect of the selective  $\beta_1$  adrenoceptor blocking agent atenolol given 100 and 200 mg once daily, was evaluated in patients with primary hypertension. The drug effected a significant reduction of BP and in the whole series there was no difference in BP on either exercise tests performed in 10 patients, or the same degree of partial  $\beta$ -blockade 24 h after intake of 100 and 200 mg atenolol. PRA during treatment with atenolol but there was no relation between the stimulated pretreatment level and the antihypertensive effect of atenolol. Side-effects were few and 35 out of 37 patients continued on atenolol treatment. Central effects were not seen.

hypertension atenolol plasma renin activity  
Scand 206 303 1979

Studies have shown a good antihypertensive effect of the selective  $\beta_1$  adrenoceptor blocking agent atenolol (Tenormin® ICI) (1, 6, 10) and long-term studies have revealed very few side-effects. A significant reduction of blood pressure (BP) has been achieved when atenolol has been administered only once daily (4, 7, 23, 28), thus posing no problem of patient compliance (12). Most  $\beta$ -adrenoceptor blocking agents depress plasma renin activity (PRA) and it has been suggested that this is one of the mechanisms of action of the antihypertensive effect of these drugs (2, 3). It has also been proposed that the antihypertensive response to propranolol can be predicted by determining the pretreatment PRA (2, 27), which would allow a more individualized antihypertensive treatment (16, 21).

One of the aims of this study was to evaluate the antihypertensive and  $\beta$  blocking effect at rest and

during exercise of atenolol administered once daily and to study the value of pretreatment renin profiling as a predictor of the antihypertensive response in patients with mild to moderate primary (essential) hypertension.

## PATIENTS AND METHODS

Thirty seven patients with primary hypertension participated in the study at three hypertension units. Secondary forms of hypertension were excluded by clinical examinations and laboratory investigations as described earlier (19). Twenty six patients had not been treated earlier and antihypertensive therapy had been withdrawn in 11 for at least one month before this study.

Patients with a supine BP  $\geq 160/95$  mmHg after a 4-week placebo period were randomized into two groups (A and B) for treatment (Table 1). Treatment periods for group A were 4 weeks on 100 mg atenolol and then 4 weeks on 200 mg, both doses administered once daily. In group B the 200 mg period preceded the 100 mg period (Fig. 1). The patients had taken their tablets about 26 hours before the last visit after 8 weeks on treatment. All visits took place at the same time in the morning (8-10 a.m.). BP was measured in a quiet room after 10 min rest in the supine position and after 2 min in the standing position. A mercury manometer was used and the diastolic pressure was registered when the Korotkoff sounds disappeared (fifth phase). All investigations at each center were performed by a highly trained nurse. Heart rate (HR) was estimated by calculating the radial pulse for 30 sec.

Ten patients were examined with dynamic work on a bicycle ergometer after 4 weeks treatment with placebo, 100 and 200 mg atenolol. All exercise tests were performed 24 hours after intake of tablets. The initial exercise load was 50 W and increased stepwise by 50 W every 4th min until subjective maximal capacity. Pulse and BP were registered after 2 and 4 min on each load. The exercise was performed in the same way after each treatment period.

Abbreviations: BP=blood pressure PRA=plasma renin activity HR=heart rate MAP=mean arterial pressure LRP=low renin hypertension

Table I Clinical data on the patients

	Group A (n=19)	Group B (n=14)
Females	10	7
Males	9	11
Age (y)		
Mean	45	50
Range	25-64	32-65
WHO I	16	17
WHO II	1	1
Earlier untreated	12	14

Before entering the study patients were classified regarding their PRA profile according to a PRA frusemide test described previously (18). During treatment, blood was drawn for analysis of upright PRA at times indicated in the design of the study.

Paired Student's *t* test and conventional regression analysis were applied in the statistical calculations.

## RESULTS

In both groups treatment with 100 and 200 mg atenolol once daily reduced BP in both supine and standing positions ( $p < 0.001$  compared to placebo for all except systolic BP on 200 mg in group B,  $p < 0.01$ ) (Figs 2 and 3). In group A treatment with 200 mg reduced BP slightly more than treatment with 100 mg (supine  $p < 0.05$ , standing  $p < 0.01$ ). No differences were noticed between BPs during the two regimens in group B.

There was a small difference in the number of responders (decrease in mean arterial pressure (MAP)  $\geq 10\%$  compared to placebo) between patients receiving 100 mg or 200 mg atenolol once daily (Table II). However, the decrease in BP in the whole patient series (groups A+B) shows no dif-

Table II Number of responders (decrease  $\geq 10\%$ )

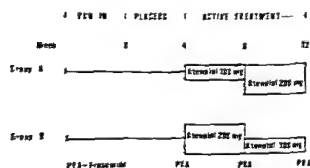
	Supine BP		Standing BP	
	100 mg	200 mg	100 mg	200 mg
Group A	13	18	13	11
Group B	10	11	10	12

ferences between the final BP on 100 mg or atenolol either supine or standing (dorm and 18/15 mmHg, respectively).

Treatment with 100 and 200 mg atenolol reduced HR in both groups (Figs 2 and 3). MAP reduced more ( $p < 0.05$ ) in group A at the visit (200 mg dose taken about 26 h before the preceding 4-week visit (100 mg given at the same morning).

The effects of atenolol given once daily on BP and HR during rest and submaximal dynamic exercise at 4 min (145 W) are shown in Figs 4 and 5. At rest there was a significant increase in MAP on both doses ( $p < 0.05$ ). During exercise MAP was 14 mm lower on both doses on placebo but these differences were not statistically significant. The decrease in HR on both doses was significant both at rest ( $p < 0.01$ ) and exercise ( $p < 0.001$ ).

Treatment with atenolol once daily decreased right PRA significantly (Table IV) except in patients in group B on 100 mg when taken about 26 h before the visit. There were no significant correlations between the antihypertensive effect of atenolol and the initial stimulated PRA in the eight patients with low renin hypertension.

Table III MAP and HR in 10 patients at rest during 4 min exercise on 145 W ( $\pm$ SD)

	Placebo	Atenolol 100 mg	Atenolol 200 mg
At rest			
MAP (mmHg)	118 $\pm$ 12	107 $\pm$ 14	104 $\pm$ 14
HR (beats/min)	79 $\pm$ 14	61 $\pm$ 10	60 $\pm$ 10
During exercise			
MAP (mmHg)	142 $\pm$ 18	128 $\pm$ 15	125 $\pm$ 15
HR (beats/min)	142 $\pm$ 12	122 $\pm$ 10	120 $\pm$ 10

\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  compared to placebo.

Fig 1 Design of the study.

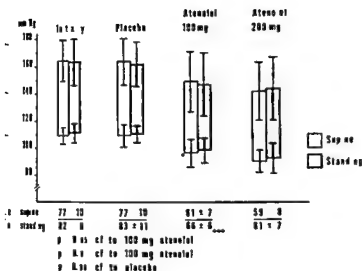


Fig. 2 Group A Supine and standing BP and HR (Y ± S.D.)

frusemide stimulated PRA  $<0.38$   $\mu$ kat/l. The decrease in MAP was only 10 compared to 16 mmHg in the eight patients with highest renin values (mean PRA 1.87 but this difference did not reach statistical significance). Effects were few: 34 patients had no complaints. Two patients reported cold extremities but they improved after dose reduction from 200 to 100 mg atenolol once daily. One patient experienced weight gain, anorexia and dyspnoea and had to be withdrawn after 4 weeks of treatment in a dose of 200 mg once daily. This patient had LHH by our definition.

## DISCUSSION

The present study clearly shows an antihypertensive and pulse-reducing effect of the selective  $\beta$ -adrenoceptor blocking drug atenolol even when given as a single daily dose to patients with uncomplicated primary hypertension. Clinically relevant BP reductions were achieved with both 100 and 200 mg given once daily. In group A, 200 mg atenolol decreased BP slightly more than 100 mg but the patients had been on treatment for a longer time (8 weeks) than on only 100 mg (4 weeks). In group B, where the initial daily atenolol dose was 200 mg, the decrease in BP was equally good when the dose after 4 weeks' treatment was reduced to 100 mg.

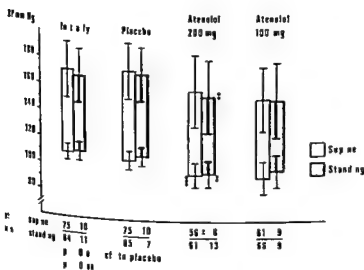


Fig. 3 Group B Supine and standing BP and HR (Y ± S.D.)

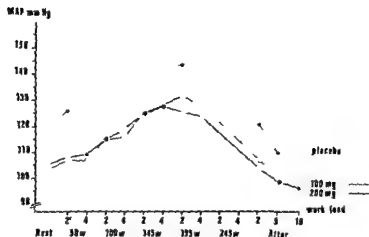


Fig 4 MAP at rest and during work load ( $n=10$ )

We have previously investigated dose-response relationships for atenolol given in doses of 100–400 mg daily (10). According to that study 200 mg a day seemed to be optimal. The present study shows that even 100 mg atenolol daily would be sufficient in most patients to reduce BP effectively, which is in accordance with other reports (4, 23, 26).

Recent treatment policy with  $\beta$  adrenoceptor blocking drugs in hypertension has focused on giving the active agent only once daily and thereby possibly increasing patient compliance (8, 17, 25). The present study was designed to explore if atenolol could be administered as a single dose in the morning. The results show that this is possible. Despite a plasma half life of 6–9 hours (5) the antihypertensive and pulse reducing effects were prolonged and seemed to be sustained for at least 24 hours both at rest and during exercise.

As the exercise tests shows 100 mg atenolol was sufficient to give a partial  $\beta$  adrenoceptor blocking

effect throughout 24 hours or more and the dose (200 mg) did not result in a higher degree of  $\beta$  blockade. This is in agreement with other studies (13, 14, 24).

Another observation indicating sympathetic nervous inhibition is the effect on the PRA during treatment (Table IV). The PRA level in upright position reflects the degree of sympathetic stimulation. As shown in Table IV patients received only 100 mg atenolol 26 hours before PRA was measured, exhibited no significant suppression of PRA. In contrast PRA suppression was demonstrated in patients in group A who had 200 mg about 26 hours before the PRA was drawn and also in both groups when PRA was measured about 2–4 hours after tablet intake. This may indicate that there are different mechanisms for the suppression of renin and the decrease in blood pressure during treatment with atenolol.

It would be an advantage in our clinical

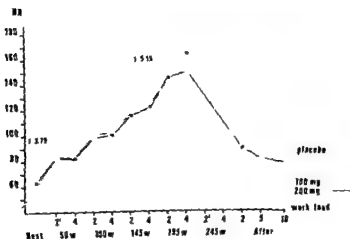


Fig 5 Mean HR (beats/min) at rest and during exercise ( $n=10$ )

PRA (plasma renin activity) before and during treatment with atenolol ( $\pm$  SEM)

In ally		Post frusemide	Placebo upright	Atenolol upright	
Supine	Upright			100 mg	200 mg
0.36	0.64	0.68	0.49	0.77*	0.13**
0.08	+0.12	+0.13	+0.13	+0.08	+0.04
0.39	0.64	1.05	0.76	0.77	0.23*
0.08	+0.11	+0.30	+0.21	+0.08	+0.06

\* $p < 0.01$  compared to upright pretreatment values

tensive treatment if there was some simple clinical marker to predict the treatment response. One clinical parameter has been proposed to do this and many authors have suggested that a high PRA level should be a marker for  $\beta$ -adrenoceptor blocking agents. Moreover it has previously been shown that  $\beta$ -blockers are almost ineffective in patients with LRH (16). Therefore we tested this in the present study. Although the decrease in BP was less in eight patients with LRH than in those with normal to high PRA, the differences were not statistically significant and there was no significant correlation between pretreatment PRA and the response to treatment (reflected from the decline in MAP). Thus renin did not predict the response to antihypertensive treatment in the present study because the number of patients with LRH was small. Another possibility is that the prediction of upright or frusemide stimulated PRA is not to be clinically relevant because many factors are involved in the maintenance of primary hypertension (9). There was no biochemical evidence that patients with higher PRA levels differed in the renal sodium balance and there was no difference in electrolyte excretion before treatment between the two groups.

The clinical usefulness of a new antihypertensive therapy is dictated by its tolerance and of side-effects. In our study atenolol was well tolerated and the side-effects were infrequent. The only relevant complaints were a decrease in peripheral blood flow as indicated by cold extremities in two patients and an increase in expiratory resistance with dyspnoea in one patient.

Central nervous side effects have been described in patients treated with non-selective  $\beta$ -blocking drugs (79). We did not notice any such effects and this agrees with a recent report demonstrating much less central nervous side effects when patients were switched from propranolol to atenolol therapy (15).

We conclude that atenolol given once daily can be used as a safe and efficient antihypertensive drug with a low frequency of side effects. A dose of 100 mg atenolol seems to be sufficient in most patients to induce reduction of BP and  $\beta$ -blockade for 24 hours.

## REFERENCES

1. Amery A, Bilet L, Boel A, Fagard R, Reybrouck T & Willems J. Mechanisms of hypotensive effect during beta-adrenergic blockade in hypertensive patients: haemodynamic and renin response to a new cardioselective agent. *Tenormin* or *ICI 66097*. *Am Heart J* 91: 634, 1976.
2. Buhler FR, Burkart F, Lutold BE, Kung M, Marbet G & Pfisterer M. Antihypertensive beta-blocker action as related to renin and age. A pharmacological tool to identify pathogenetic mechanisms in essential hypertension. *Am J Cardiol* 36: 653, 1975.
3. Buhler FR, Laragh JH, Baer L, Vaughan ED & Brunner HR. Propranolol inhibition of renin secretion: A specific approach to diagnosis and treatment of renin-dependent hypertension diseases. *N Engl J Med* 287: 1219, 1972.
4. Castleden CM, Dahan JR & George CF. A comparison of once and twice daily atenolol in hypertension. *Postgrad Med J* 43: 679, 1977.
5. Conway FJ, Fitzgerald JD, McAlinsh J, Rowlands DJ & Simpson WT. Human pharmacokinetic and pharmacodynamic studies on atenolol (ICI 66082), a new cardioselective beta-adrenoceptor blocking drug. *Br J Clin Pharmacol* 3: 267, 1976.
6. Dollery CT, Lewis G & Myers MG. Clinical

- evaluation of a new beta adrenoceptor antagonist ICI 66 082 in essential hypertension *Br J Clin Pharmacol* 2 185 1975
- 7 Douglas-Jones A P & Cruickshank J M Once daily dosing with atenolol in patients with mild or moderate hypertension *Br Med J* 1 990 1976
  - 8 Frithz G Pindolol once daily in the treatment of hypertension *Ups J Med Sci* 81 151 1976
  - 9 Guyton A C Coleman T G Cowley A W Scheel K W Manning R D & Norman R A Arterial pressure regulation: Overriding dominance of the kidneys in long term regulation and in hypertension. In *Hypertension manual* (ed J H Laragh) p 111. Yorke Medical Books, New York 1974
  - 10 Hansson L Åberg H Karlberg B E & Westerlund A Controlled study of atenolol in treatment of hypertension *Br Med J* 2 367 1975
  - 11 Hansson L Henningsen N C Karlberg B E Åberg H Westerlund A Gudbrandsson T & Jamesson S Long term trial of atenolol in hypertension *Curr Ther Res* 22 839 1977
  - 12 Harris A M Woollard K V & Tweed J A A study of once daily Tenorman (atenolol) in hypertension. Some implications in patient compliance *J Int Med Res* 4 344 1976
  - 13 Harry J D The demonstration of atenolol as a beta adrenoceptor blocking drug in man *Postgrad Med J (Suppl)* 3 65 1977
  - 14 Harry J D & Shields A G Relative activity of atenolol and metoprolol *Br Med J* 2 128 1978
  - 15 Henningsen N C & Mattasson I Long term clinical experience with atenolol—a new selective  $\beta_1$  blocker with few side-effects from the central nervous system *Acta Med Scand* 205 61 1979
  - 16 Karlberg B E Kågedal B Tegler L Tolagen K & Bergman B Controlled treatment of primary hypertension with propranolol and spironolactone: a crossover study with special reference to initial plasma renin activity *Am J Cardiol* 37 642 1976
  - 17 Karlberg B E Nilsson O Tolagen K Nitelius E & Waern U Once daily treatment with metoprolol in primary hypertension. Effects on blood pressure in relation to plasma renin activity, urinary aldosterone excretion and the concentration of metoprolol in plasma *Clin Pharmacol Ther* 1979
  - 18 Karlberg B E & Tolagen K Relationship between blood pressure, age, plasma renin and electrolyte excretion in normotensive subjects *J Clin Lab Invest* 37 521 1977
  - 19 — Age, blood pressure, renin and angiotensin in primary hypertension and in the normal state *Scand J Clin Lab Invest* 38 319 1977
  - 20 Laragh J H Vasoconstriction volume: a new understanding and treating hypertension. Renin and aldosterone profiles *Am J Med* 1973
  - 21 — The classification and treatment of hypertension using the renin volume and vasoconstriction volume analysis *J Hypertens* 137 184 1975
  - 22 Lund Johansen P Haemodynamic effects of a new beta adrenoceptor blocking drug (ICI 66 082) in essential hypertension *Clin Pharmacol* 3 445 1976
  - 23 Marshall A J Barritt D W & Harris J Response and frequency of admission rate in essential hypertension—once daily treatment with beta blockade *Postgrad Med J (Suppl)* 3 1977
  - 24 Noer G H & Ikelä T Atenolol in hypertension *Curr Ther Res* 24 17 1978
  - 25 Reybrouck T Amery A Fagard R & Lijnen P & Meulepas E Beta-blockade three times a day *Br Med J* 1 1786 1978
  - 26 De Tollenaere G & Verdonck G E Atenolol administered once daily in hypertension *Acta Therapeutica* 2 31 1977
  - 27 Weber M A Drayer J & Laragh J Renin predicts and aldosterone determines the antihypertensive treatment *Circulation* 55 31 1977
  - 28 Wilcox R G Randomised study of a beta-blocker and a thiazide diuretic in essential hypertension *Br Med J* 2 383 1978
  - 29 Zacharias F J Cowen K J Pratt J & Wall B G Propranolol in hypertension: long term therapy 1964–1970 *Am Heart J* 1972

# 10 Acid Metabolism in Patients with a Hereditary Myopathy and Paroxysmal Myoglobinuria

John Wahren Håkan Linderholm and Philip Felig

Departments of Clinical Physiology Huddinge Hospital Huddinge and Urology Hospital Uresä, Sweden  
 Department of Internal Medicine Yale University School of Medicine New Haven Conn USA

**CT** Amino acid metabolism of skeletal as examined in two patients with a hereditary myopathy associated with elevated blood lactate and pyruvate and paroxysmal myoglobinuria. Arterial concentrations as well as exchange respectively of amino acids, pyruvate and oxygen were studied at rest and during exercise (16 and 33 W) using a bicycle ergometer. In the resting state the arterial concentrations of amino acids and pyruvate in the resting state were similar to those of healthy controls. During exercise a decrease in lactate and pyruvate concentrations was seen in the patients exceeding the small fall in healthy controls. The arterial alanine concentration during exercise in both patients (+120%) while no change was observed in the controls working at the same work load. No other amino acid showed a consistent rise during exercise. In the arterial levels of the branched chain amino acids (leucine, isoleucine) fell during exercise in the patients but not in the controls. Net release of alanine from the legs in patient 1 rose 2.5- and fivefold during exercise while no change was seen in the controls. Alanine output from the working arms in patient 2 exceeded that of controls by 50%. In addition, release of lactate and pyruvate during exercise was much augmented in both patients in comparison to controls. It is concluded that the rate of formation by skeletal muscle during exercise is increased in patients with this type of myopathy associated with elevated levels of lactate and pyruvate. These findings lend support to the theory that carbon skeletons for alanine synthesis by muscle are derived from muscle glycolysis.

muscle phosphorylase (10). A less well recognized hereditary myopathy in which myoglobinuria also occurs (6) is associated with abnormalities in muscle glycolysis. In response to mild exertion these patients show a much increased release of pyruvate and lactate from working muscle (7).

Studies in normal man have demonstrated that exercise stimulates the formation and release of alanine by muscle. Release of alanine exceeds that of all other amino acids and is proportional to the circulating level of pyruvate (4). These and other observations have led to the formulation of the glucose-alanine cycle whereby alanine formation and release from muscle is determined at least in part by the availability of glucose derived pyruvate (3, 4). In keeping with this relationship a diminished formation of alanine by muscle has been observed in patients with McArdle's syndrome in whom pyruvate availability is reduced (14). It is not known whether this relationship between pyruvate availability and alanine formation applies equally to circumstances of hyperpyruvicemia. The present study was consequently undertaken to examine alanine metabolism in patients with a hereditary myopathy and hyperpyruvicemia as a means of further characterizing this disorder.

## SUBJECTS AND METHODS

Two patients with a hereditary myopathy associated with elevated blood levels of lactate and pyruvate and paroxysmal myoglobinuria were studied. This disorder has previously been described in five families in Northern Sweden (6, 7). The patients were siblings with healthy parents.

### Patient 1

A 20-year-old non-obese female. Since the age of 17 she had been easily fatigued even by light exertion and could walk only about 100 m on flat ground. Her symptoms progressed with the addition of palpitations, dyspnea and

of alanine amino acid myopathy myoglobinuria muscle lactate pyruvate  
 Acta Med Scand 206 309 1979

Myoglobinuria is a known complication of McArdle syndrome a disorder characterized by lack of



Table I Circulatory and hemodynamic data at rest and during leg exercise for patient 1

	Exercise		
	Rest	16 W	33 W
Pulmonary oxygen uptake (ml/min STPD)	240	484	637
Expiratory exchange ratio	0.81	1.33	1.39
Heart rate (beats/min)	70	150	181
Arterial oxygen content (ml/l)	167.8	184.2	188.7
A-FV oxygen difference (ml/l)	44.8	42.2	29.4
Hematocrit	40	44	45
Estimated leg blood flow (l/min)	0.65	6.4	14.5

\* Arterial femoral venous

muscle pain after exercise at times with vomiting after heavier exercise. The symptoms became progressively more marked and she had periods of pain in the back and shoulder muscles even in the resting state. Dark urine was observed but myoglobinuria was not definitely established.

She was hospitalized (University Hospital Umeå, Sweden) at the age of 18 and showed a low physical working capacity (heart rate 170 beats/min at a bicycle work load of 30 W) as well as high pyruvate (0.24–0.35 mmol/l) and lactate (2.2–4.3 mmol/l) concentrations in arterial blood. The maximum voluntary isometric force

of several muscle groups including the legs was normal.

A few months later she suffered an acute attack with generalized muscle pain, vomiting, dizziness, excessive fatigue. On re-admission to the hospital, metabolic acidosis and high blood concentrations of lactate, pyruvate and transaminases. Myoglobin was not observed. These symptoms gradually subsided over a period of 4–6 weeks and left no marked sequelae.

At the time of the present study she still had easy fatigability and muscle pain upon exertion. Therefore her physical working capacity was low, at only 30 W resulting in a heart rate of 170 beats/min.

#### Patient 2

A 22-year-old non-obese male who had always been physically fit than his classmates. During his life at 20 years of age, muscle pain and fatigue prevented him from participating fully in activities involving heavy exercise. His condition deteriorated gradually, appearance of muscle pain in the resting state during muscle strength. Red urine was observed on occasions. He was hospitalized with generalized muscle pain and weakness and gradually developed pain in the leg muscles, subsequently extending to the arm muscles and other muscle groups. He required medical treatment and electroconvulsion for ventricular tachycardia and fibrillation. Myoglobinuria was documented. After this episode he gradually recovered but had persisting paresis and atrophy of the right muscle of both legs and became bound to a wheelchair.

At the age of 22 he was examined at the University

Table II Arterial concentrations and leg exchange of amino acids ( $\mu\text{mol/l}$  and  $\mu\text{mol/min}$ ) and lactate (mmol/l and mmol/min) at rest and during leg exercise in patient 1 (P) and healthy control (mean  $\pm$  S.E.M.)

	Arterial concentration						Leg exchange				Extra	
	Exercise											16 W
	Rest		16 W		33 W		Rest		P			
	P	C	P	C	P	C	P	C				
Taurine	25	37± 4	24	31± 3	26	31± 3	0	0±0	-4			
Threonine	60	116± 5	53	93±11	52	91± 9	-1	-3±1	1			
Serine	64	124±15	54	91±10	51	94±11	2	4±1	29			
Proline	146	218±27	144	201±23	142	201±20	8	-5±3	-11			
Glycine	206	211±19	198	163±13	202	162±13	-9	-2±1	-64			
Alanine	218	187±15	404	172±16	531	171±14	-26	-16±4	4			
α Aminobutyrate	13	30± 6	12	23± 5	10	23± 4	0	0±1	4			
Valine	260	234±26	242	186±20	233	183±17	5	2±2	7			
Cystine	87	110±11	85	75± 6	80	76± 9	1	6±2	7			
Methionine	17	18± 2	21	16± 2	17	17± 1	-3	-1±1	11			
Isoleucine	93	66±10	88	54± 7	77	54± 6	1	-1±1	11			
Leucine	151	123±15	136	99±12	121	100±10	2	-1±1	-8			
Tyrosine	48	46± 5	49	38± 5	46	37± 4	-1	-1±1	-8			
Phenylalanine	52	46± 4	48	38± 3	51	45± 9	0	-1±1	-0.40			
Pyruvate	0.133	0.059±0.006	0.665	0.062±0.005	0.890	0.067±0.078	-0.001	-0.002±0.001	-1.14			
Lactate	1.00	0.76±0.11	7.27	0.91±0.19	11.47	0.94±0.20	-0.08	0.03±0.02				

Load Exercise tests on a bicycle ergometer arms (cranking) showed a high heart rate already at work loads (33 W) and high concentrations of lactate (2.2 mmol/l) and pyruvate (0.46 mmol/l) in arterial

data for patient 1 were obtained from the study of et al (14). Three healthy non obese volunteers performed arm exercise and served as controls for patient 1. Patients and all controls were informed of the purpose and possible risks involved in the study and gave their consent to participate.

Experiments were examined in the postabsorptive state at the supine position and during upright exercise on a bicycle ergometer working with the legs (pat 1) and with the arms (pat 2). Teflon catheters were introduced percutaneously into the brachial or femoral artery and into the axillary vein. The tip of the femoral venous catheter was placed close to the inguinal ligament and that of the axillary venous catheter just outside the thoracic cage under fluoroscopic control.

Patients exercised for 7-8 min at work loads of 16 and 33 W. Blood samples for analysis of oxygen, lactate, pyruvate and amino acid concentrations were drawn at the end of each work load during exercise. In addition, arterial and pulmonary oxygen uptake were determined during exercise.

Arterial oxygen uptake was measured using a Fick principle and the Scholander micro-technique. Heart rate was determined from the ECG. Leg blood flow was calculated from the pulmonary oxygen uptake and the

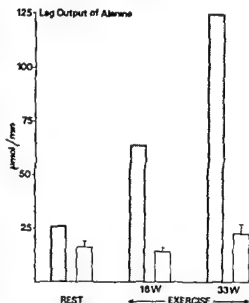


Fig. 1. Leg output of alanine in patient 1 (hatched bars) and controls (white bars) in the resting state and during bicycle exercise at 16 W and 33 W (mean  $\pm$  S.E.M.).

arterial femoral venous (A-FV) oxygen difference according to the formulas given by Jorfeldt and Wahren (5). Blood flow to the exercising arms was calculated on the assumption that 80% of the increment in oxygen uptake during exercise is utilized by the working arm muscles. Arm blood flow at rest was assumed to be 0.5 l/min. The methods employed for the determinations of lactate, pyruvate, individual plasma amino acids and hemoglobin concentration as well as oxygen saturation and hematocrit have been described previously (4, 7, 13).

All data in the text, tables and figure are given as mean  $\pm$  S.E.M.

## RESULTS

### Patient 1

In the resting state patient 1 showed a normal pulmonary oxygen uptake and heart rate (Table I). The A-FV oxygen difference was slightly decreased and the estimated leg blood flow was approximately 40% greater than reported for healthy subjects (5). In response to exercise the pulmonary oxygen uptake rose in a normal manner in relation to the work but the rise in heart rate was much increased. The estimated leg blood flow rose 10-fold above basal during exercise at only 16 W and increased more than 20-fold at 33 W.

The arterial concentrations and the leg exchange of amino acids, lactate and pyruvate in the patient and healthy controls are given in Table II. The

Table III Circulatory and hemodynamic data at rest and during arm exercise for patient 2 and control subjects

	Patient 2			Controls					
	Rest	Exercise		Rest		Exercise 33 W		Exercise 108 W	
		16 W	33 W	Mean	Range	Mean	Range	Mean	Range
Pulmonary oxygen uptake (ml/min)	285	696	1 106	280	260-292	877	804-964	2 100	1 400-2 800
Expiratory exchange ratio	0.74		1.11	0.83	0.77-0.89	0.88	0.79-0.96	1.04	0.84-1.24
Heart rate (beats/min)	60	163	196	56	52-69	82	74-90	166	140-190
Arterial oxygen content (ml/min)	202	215	227	178	171-185	180	176-185	190	175-205
A-V oxygen difference (ml/min)	51.1	66.9	73.9	64	52-73	126	122-131	171	157-185
Arterial pH	7.41	7.37	7.30	7.41	7.36-7.47	-	-	7.33	7.25-7.41
Estimated arm blood flow (l/min)	0.5	4.9	8.9	0.5		3.8		17.0	

arterial levels in the basal state were all within the normal range (4-7). During exercise the patient's arterial concentration of lactate and pyruvate rose sharply. Arterial alanine was the only amino acid for which a marked increase was observed. During work at 16 W the alanine concentration rose to approximately 70% and at 33 W to as much as 125% above basal, whereas for healthy controls exercising at an identical work load no rise was detected (Table II). No other amino acid showed a consistent rise in arterial concentration during exercise. Instead the arterial level of several others, notably the branched chain amino acids valine, isoleucine and leucine, fell during work and positive A-FV differences were seen, indicating net leg uptake of these amino acids.

The net exchange of substrates for the leg was estimated from the product of leg blood flow and the A-FV differences. The leg output of lactate for patient 1 and controls is shown in Fig. 1. In the basal state the patient's output exceeded that of controls by 60%. This difference became greater during exercise: the leg output of lactate rose 2.5- and 5-fold during work at 16 and 33 W, respectively, whereas no significant change from the basal level was seen in the controls at the equal work loads. In the patient a net uptake of leg tissues of the amino acids proline, isoleucine and leucine was noted during exercise (Table II). Lactate and pyruvate output rose sharply in the patient in response to exercise (Table II). In contrast, the healthy

Table IV Arterial concentrations of alanine, pyruvate and lactate in patient 2 (P) and 10 control subjects (C) at rest and during arm exercise (mean and range)

	Rest	Exercise		
		16 W	33 W	108 W
Alanine ( $\mu\text{mol/l}$ )				
P	170	262	374	
C	215 (206-223)		301 (288-313)	441 (381-500)
Pyruvate ( $\text{mmol/l}$ )				
P	0.10	0.34	0.47	
C	0.11 (0.10-0.11)		0.16 (0.14-0.18)	0.31 (0.28-0.34)
Lactate ( $\text{mmol/l}$ )				
P	0.80	4.60	9.15	
C	0.66 (0.61-0.73)		1.49 (1.27-1.91)	8.55 (5.9-11.8)

only a small output of lactate and pyruvate working legs at this light work load. The lactate output observed in the patient was even less than the value reported for healthy subjects at similar work loads ( $4.0 \pm 0.8$  mmol/min) (15).

Increased pulmonary oxygen uptake and heart rate were found in the resting state (II). During arm exercise at 16 and 33 W, oxygen uptake and heart rate both rose sharply, reaching 196 beats/min during exercise. The estimated arm blood flow in patient 2 was increased during exercise and exceeded that of the controls working at an equal level. Arterial concentrations of alanine, lactate and pyruvate in patient 2 were within normal ranges at rest (Table IV). In response to arm exercise, however, the patient's arterial levels of lactate and pyruvate rose substantially more than the controls and quite out of proportion to load (7). In the patient the arterial level of lactate was approximately 120% above the basal value during exercise at 33 W, the corresponding increase in the controls being 40%. Alanine output from exercising arms (33 W) in patient 2 was  $1.2 \mu\text{mol/min}$ , which exceeded the normal value for the controls ( $0.78 \pm 0.10$ ) by 140%. Only during exercise at 108 W did the controls reach arterial concentrations of pyruvate and lactate comparable to those in the patient during work at 33 W. No amino acid from alanine showed a rise in arterial concentration or a net release during exercise; instead the concentrations of threonine, methionine, cystine, isoleucine, leucine and valine tended to fall.

## DISCUSSION

The differences in arterial concentration and net release of alanine from muscle during exercise in the patients differ distinctly from those for the controls. The rise in arterial alanine concentration in both patients was more marked than in the healthy subjects at similar work loads. The observed differences are far greater than the errors involved in the determination of alanine concentration. Moreover, the estimated release of alanine from the working leg and arm

respectively indicates that exercise induced by hyperalaninemia in these patients is the result of a markedly augmented formation and release of alanine from working muscle (Fig. 1).

With regard to the mechanism of alanine formation it is noteworthy that the patients developed a marked hyperpyruvicemia and showed an augmented release of both pyruvate and lactate from muscle during exercise. Although measurements of intramuscular pyruvate concentrations were not feasible in this study, the present findings suggest that the intracellular availability of pyruvate was much increased during exercise. The augmented release of alanine from muscle and the elevated arterial concentrations of alanine during exercise in these patients thus lend strong support to the existence of a glucose-alanine cycle, as suggested previously, whereby alanine formation in muscle is determined in part by glucose derived pyruvate availability (3, 4, 14). Recent studies with the rat diaphragm have further supported the theory that the carbon skeletons for alanine formation by muscle are derived from muscle glycolysis (2).

As to the source of amino groups for alanine synthesis, the branched chain amino acids (valine, leucine and isoleucine) which are catabolized primarily in muscle (8, 9) have been postulated to provide the nitrogen source for alanine formation in muscle (1, 4). This has recently received experimental support from studies demonstrating that the addition of branched chain amino acids increases alanine formation by the isolated rat diaphragm (2, 11, 12). In agreement with this, the augmented alanine production by our patients was accompanied by a fall in the arterial levels of valine, leucine and isoleucine. This phenomenon, which was not observed in the healthy controls, suggests that in the patients branched chain amino acids were taken up and degraded by working muscle thereby providing amino groups for transamination of pyruvate to alanine.

The transamination of branched chain amino acids in muscle involves the formation of  $\alpha$ -ketoacids. These may subsequently undergo oxidation thereby yielding 32–43 mol ATP per mol amino acid (11). Besides contributing to alanine production, branched chain amino acid catabolism may thus be a significant source of energy for muscle in this disorder. While the primary biochemical defect in the present type of myopathy remains to be established, the current findings indicate that

increased formation and accumulation of alanine accompany the elevations in arterial lactate and pyruvate concentrations. Thus it may be postulated that increased formation of alanine in these patients reflects a compensatory mechanism whereby accelerated catabolism of branched chain amino acids provides an alternative energy yielding process.

During the light exercise employed in the present study, both of the patients developed disproportionate tachycardia, hyperkinetic circulation and hyperventilation as well as symptoms of fatigue, palpitations and local pain in the working muscles. All of these findings reflect other aspects of this disorder and are in good agreement with previous reports (7).

### ACKNOWLEDGEMENTS

This study was supported by grants from the Swedish Medical Research Council (4X 3108) from the National Institutes of Health (AM 13526) and from the University of Umeå. Dr Felig is an Established Investigator of the American Diabetes Association.

### REFERENCES

- 1 Buse M G, Biggers J F, Frederici K H & Buse J F. Oxidation of branched chain amino acids by isolated hearts and diaphragms of the rat. *J Biol Chem* 247: 8085, 1972.
- 2 Chang T W & Goldberg A L. The origin of alanine produced in skeletal muscle. *J Biol Chem* 253: 3677, 1978.
- 3 Felig P, Pozefsky T, Marliss E & Cahill G F Jr. Alanine: Key role in gluconeogenesis. *Science* 167: 1003, 1970.
- 4 Felig P & Wahren J. Amino acid metabolism in exercising man. *J Clin Invest* 60: 701, 1977.
- 5 Jorfeldt L & Wahren J. Leg blood flow during exercise in man. *Clin Sci* 41: 439, 1971.
- 6 Larsson L E, Linderholm H, Mjølhus J, qvist T & Sörms R. Hereditary metabolicopathy with paroxysmal myoglobinuria & normal glycolysis. *J Neurol Neurosurg* 27: 361, 1964.
- 7 Linderholm H, Muller R, Ringqvist T & R. Hereditary abnormal muscle metabolism: hyperkinetic circulation during exercise. *Scand J Clin Lab Invest* 185: 153, 1969.
- 8 Manchester K L. Oxidation of amino acids in isolated rat diaphragm and the influence of calcium. *Biophys Acta* 100: 295, 1965.
- 9 Miller L L. The role of the liver and the tissues in the regulation of free amino acid in the blood. In: *Amino acid pools: Distribution and function of free amino acids* (Holden H, ed.) pp 708-728. Elsevier, Amsterdam, 1959.
- 10 Mommaerts W F H M, Billingworth B C M, Guillory R J & Seraydarian K A. A disorder of muscle associated with the phosphorylase. *Proc Natl Acad Sci USA* 1959.
- 11 Odessey R, Kjarallah E A & Goldberg. Origin and possible significance of alanine produced by skeletal muscle. *J Biol Chem* 249: 63, 1974.
- 12 Palaiologos G & Felig P. Effects of ketosis on amino acid metabolism in isolated rat diaphragm. *Biochem J* 154: 709, 1976.
- 13 Wahren J, Felig P, Ahlborg G & Jorfeldt L. Glucose metabolism during leg exercise in man. *Invest* 50: 2715, 1971.
- 14 Wahren J, Felig P, Havel R J, Jorfeldt L, Pernow B & Saltin B. Amino acid metabolism in McArdle's syndrome. *N Engl J Med* 287: 100, 1972.
- 15 Wahren J, Saltin B, Jorfeldt L & Felig P. Influence of age on the local circulation during leg exercise. *Scand J Clin Lab Invest* 33: 7, 1975.

# Pernicious Anaemia as a Risk Factor in Gastric Cancer

Lars Elsborg and Johannes Mosbech

*From the Department of Medicine, Copenhagen County Hospital St. Elisabeth, Copenhagen, Denmark*

**OBJECT** In order to assess the risk of gastric (GC) developing in patients with pernicious (PA) the prevalence of PA was analysed in patients with GC notified to the Danish Cancer Registry in 1972. Among 877 patients with GC, PA previously been diagnosed in 19 (2.2%). In seven PA had been diagnosed only shortly before recording, the diagnosis of PA could be regarded as unquestionable only in the remaining 12 (1.3%). In either case the frequency of PA was only higher than in a reference group of patients with cancer of the colon who had been selected the same way. Calculation of the incidence of GC in patients showed that this was about three times higher than in the general population. The annual GC was calculated to be 0.3%. In PA patients the tumour was primarily localized to the body and of the stomach, whereas it mainly involved the fundus and pyloric region in patients without PA. In view of the low cancer rate it is concluded that gastroscopy and barium meal examination indicated in PA patients in general. Whenever patients with PA complain of dyspepsia, examination with gastroscopy and barium meal should how- ever be carried out on liberal indications.

**KEY WORDS:** cancer risk, gastric cancer, pernicious

Acta Med Scand 206 315 1979

Prevalence of pernicious anaemia (PA) in Denmark has been found to be 1/31 000 (1/71 000 in men and 1/81 000 in women) (9). From these figures it is estimated that in the country as a whole there are about 6 000 patients with PA. Patients with PA are at an excess risk of developing gastric cancer (3, 8). It is generally estimated that the risk is three times as high as in the general population, but the incidence of GC among PA patients has not been reported in the literature (2). Only Gregor et al. (5) reported an incidence of GC in a series of PA patients followed for a period of 15 years.

A difficulty in studies of this kind is that relatively large series of patients with PA have to be followed over long periods in order to establish a reasonably reliable incidence. Furthermore, the overall morbidity from GC is falling in the western world. In Denmark it has been reduced to almost one half within the last decade (7).

We have therefore chosen to study the prevalence of PA in a series of patients with GC. This prevalence is compared with that of PA in control patients with cancer of the colon.

## PATIENTS AND METHODS

Based on a list of cases of GC notified to the Danish Cancer Registry in 1972, inquiries were sent to the Danish hospital departments where these patients had been treated. To a total of 998 inquiries, 898 replies (94%) were received with case records or discharge summaries. However, 21 of the patients had to be excluded because of uncertain diagnoses. In the remaining 877 patients the diagnoses had been established by biopsies at operation in 60%, by autopsy in 28%, by gastroscopy and biopsy in 6%, while the diagnoses were based exclusively on barium meal examinations in 4% and on other methods, such as lymph node biopsy or bone marrow studies, in 2%.

The series consisted of 533 men and 344 women. The tumour was localized to the prepyloric region in 59%, to the body of the stomach in 30%, whereas it involved the fundus in 11% only.

The reference series was selected on the basis of a list of cases of cancer of the colon notified to the Danish Cancer Registry during 1970. It consisted of 1 777 patients—902 men and 875 women—with verified cancer localized to the colon or rectum.

The statistical analysis of the data is based on the  $\chi^2$  test.

**Reprint requests to:** J. Mosbech, M.D., Department of Medicine, Copenhagen County Hospital St. Elisabeth, Hans Bogbinders Allé 3, DK-2300 Copenhagen S, Denmark.

**Abbreviations:** GC=gastric cancer, PA=pernicious anaemia.

Table I Age and sex distribution of patients with GC cancer of the colon and PA

Age (y)	GC				PA + GC				Cancer of the colon				PA of the 2
	Women		Men		Women		Men		Women		Men		Women (%)
	N	%	N	%	N	%	N	%	N	%	N	%	
20-29	2	0.6	0		0		0		5	0.6	4	0.4	0
30-39	6	2	5	0.9	0		0		11	1	7	0.8	0
40-49	10	3	21	4	0		0		40	5	36	4	0
50-59	26	8	62	12	0		2	22	115	13	117	13	0
60-69	68	20	171	32	3	30	2	22	246	28	302	33	0
70-79	165	48	193	36	5	50	3	34	313	36	285	32	1
80-89	65	19	75	14	2	20	2	22	132	15	139	15	0
>90	2	0.6	6	1	0		0		13	1	12	1	0
Average	71		70		73		70		69		68		
Range	26-93		31-93		66-84		54-87		21-101		24-93		
Total (n)	344		533		10		9		875		902		1

## RESULTS

It appears from Table I that the age distribution of patients with GC is skew showing no difference between men with GC and patients with cancer of the colon.

In 19 patients (9 men and 10 women) PA had been diagnosed prior to GC. In 11 of these patients bone marrow studies, haematological examinations or determinations of the serum level of cobalamin had verified the diagnosis of PA. In the other eight patients it was not possible to establish the criteria on which the diagnoses had been based, mainly because they had been made elsewhere and much earlier than the diagnosis of GC. The age distribution of these 19 patients, duration of PA and sites of the gastric tumours are recorded in Table II. In 11 of the 18 autopsied patients the tumour was localized to the body and fundus of the stomach. All patients had received parenteral vitamin B<sub>12</sub> injections, either of a depot preparation (Betolovex<sup>®</sup>) or hydroxocobalamin (Vibeden<sup>®</sup>).

The majority of patients with PA and GC were over 60 years (Table I), i.e. the age distribution of PA patients was also skew. However, the average ages in the four groups of patients compared were roughly the same.

In the group of men aged 50-59 years, two out of 62 (3.2%) with GC also had PA; this incidence is higher than that of PA in the reference group (0 out of 117). Similarly, the age groups 60-69, 70-79 and 80-89 years showed an overrepresentation of PA among the GC patients compared with the reference groups. In the total group with GC we found that

PA (19 out of 877) occurred with a frequency of 2.2% (1.3-3.4% at the 95% confidence limit). The reference group, the frequency of PA (1 out of 1777) was 0.2% (0.0-0.5% at the 95% confidence limit), which corresponds to the expected frequency of 0.13% in the general population. The frequency of PA in patients with GC is significantly higher than in the reference group ( $p < 0.01$ ). In the general population, for the country as a whole, it can be calculated that in 1972 about 6000 patients suffered from PA (9). Based on the total number of cases of PA and co-existing GC in 1972, it can be calculated that GC will occur in association with PA with an incidence of approximately 3.2/1000 patients with PA. In a population of 1000 patients, more than one half (54%) will be aged 70 years or more (9). In this age group, a total of 12 patients had GC associated with PA; the incidence was 3.7/1000 patients with PA (12 of 6000  $\times$  0.54) (1.9-6.5/1000 at the 95% confidence limit). As the 5-year survival rate for patients with GC within this age group is very low, this incidence can be directly compared with the mortality from GC within the same age group in the general population, which has been estimated as 1.3/1000 (1.2-1.4/1000).

## DISCUSSION

The purpose of this analysis was to assess the risk of GC developing in PA patients. We chose to analyse the prevalence of PA in a series of patients with GC and found that 2.2% of them had PA.

Table 1 Patients with PA and co-existing GC distributed according to sex, age, duration of symptoms and the tumour

Sex	Age (y)	Duration of symptoms (y)	Site of tumour
♀	84	10	No autopsy
♀	72	20	Greater curvature
♀	66	8	Greater curvature
♀	75	37	Linitis pl. greater curvature + fundus
♀	78	10	Greater curvature
♀	84	1	Prepyloric
♀	77	1	Prepyloric
♀	73	10	Greater curvature
♀	67	30	Greater curvature
♀	72	1	Prepyloric
♂	84	15	Greater curvature
♂	54	9	Greater curvature + fundus
♂	87	1	Greater curvature + fundus
♂	72	1	Prepyloric
♂	72	12	Greater curvature
♂	72	9	Greater curvature
♂	55	6	Greater curvature + fundus
♂	69	1	Prepyloric
♂	66	1	Prepyloric

about 13 times higher than that observed in the reference group in which the prevalence of PA is of the same order as in the general population. These series are corrected for the possibility that some of the patients may have had a megaloblastic anaemia secondary to GC (all patients in whom the duration of PA was less than 5 years excluded). The prevalence of PA in the GC group is 4.0%, i.e. eight times as high as that expected in the reference group. This overrepresentation of PA among GC patients gives evidence that the risk of developing GC is significantly higher among PA patients than in the general population. The annual cancer rate (19 out of 6000) is therefore low (0.3%) compared with results of other studies in which the overall risk has been estimated to be 2.3% (5).

Among patients without PA the tumour was localized to the antral and pyloric region in more than half of the cases. By contrast only one of the patients with PA had cancer involving the antral region. If in addition one excludes patients with a disease duration of less than 5 years in whom the diagnosis of PA was questionable the cancer was localized to the body and fundic region in all cases but one. This observation strongly supports the assumption that GC in all patients with PA is a pathogenesis differing from that of other

cases of GC. In this connection it has been emphasized that the atrophic gastritis which in PA patients always involves the fundus and to a varying extent the body and pyloric antrum of the stomach (3) may predispose to the development of GC (10-12). In PA extremely high gastrin concentrations are often present in the serum and gastric mucosa (1). As gastrin is a trophic hormone for the fundus of the stomach it is reasonable to assume that a causal relationship may exist between the high gastrin levels and GC in PA patients (4).

Even though the risk of cancer is significantly higher in PA patients than in the population in general routine gastroscopy or barium meal examination cannot be recommended in these patients. For each cancer disclosed it would be necessary to examine 300-600 patients which in addition to the drain on resources would give rise to considerable mental strain in the individual patient. On the other hand as atrophic gastritis does not produce symptoms any patient with PA in whom dyspepsia occurs should be subjected to gastroscopy and barium meal examination.

#### ACKNOWLEDGEMENT

This investigation was supported by a grant (no. 864/1976) from the Danish Cancer Society.



## REFERENCES

- 1 Brandsborg M, Elsborg L, Andersen D, Brandsborg O & Bastrup Madsen P. Gastrin concentrations in serum and gastric mucosa in patients with pernicious anaemia. *Scand J Gastroenterol* 12: 537 1977
- 2 Chanarin I. The megaloblastic anaemias. pp 492-496. Blackwell Scientific Publications, Oxford 1969
- 3 Elsborg L, Andersen D, Ellegaard J, Myhre Jensen O & Bastrup Madsen P. Gastric mucosal polyps in pernicious anaemia. *Scand J Gastroenterol* 12: 49 1977
- 4 Ganguli P C, Cullen D R & Irvine W J. Radioimmunoassay of plasma gastrin in pernicious anaemia, achlorhydria without pernicious anaemia, hypochlorhydria and in controls. *Lancet* i: 155 1971
- 5 Gregor O, Bláha J, Merth I, Svoboda M, Cholt M, Bednar B & Reinauer R. Gastric cancer detection among risk groups and their longitudinal follow up. Abstr vol p 349. X Int Congr Gastroenterol, Budapest 1976
- 6 Jørgensen J. Den perniciøse anæmi og holdelsesbehandling og prognose i Danmark. *Acta Med Scand* 1949
- 7 Mosbech J. Cancer ventriculi. *Lancet* i: 139 1973 1977
- 8 Mosbech J & Videbaek Aa. Mortality and risk of gastric carcinoma among patients with pernicious anaemia. *Br Med J* 2: 390 1970
- 9 Pedersen A B & Mosbech J. Mortality in pernicious anaemia. *Acta Med Scand* 184: 449 1973
- 10 Siurala M, Kekki M, Ihamaki T, Sarna S, Lehtola J, Saukkonen M, Isokoski M & K. Genetic and dynamic aspects on the risk between atrophic gastritis and pernicious anaemia and gastric carcinoma. *Scand J Gastroenterol* 12: 45-97 1977
- 11 Torgersen J. Localization of gastrin and cancer, especially in cases of pernicious anaemia. *Radiol (Stockh)* 25: 845 1944
- 12 Walker I R, Strickland R C, Ungar B & Walker I R. Simple atrophic gastritis and gastric cancer. *Gut* 12: 906 1971

# Relief of Pruritus as an Early Sign of Spinal Cord Compression in Hodgkin's Disease

H. Olsson and L. Brandt

From the Department of Oncology, University Hospital, Lund, Sweden

**ACT** In a patient with advanced Hodgkin's disease (HD) associated with generalized pruritus, an early relief of itching was found to be an early sign of spinal cord compression. Following irradiation of an extradural mass at the Th II level, itching disappeared. Although the mechanisms bringing about relief of pruritus in HD are unknown, the relief and recurrence of this symptom in our patient are in line with a local origin of pruritus in the disease. Spontaneous relief of pruritus in HD despite other signs of disease should prompt a neurological examination. Early recognition and treatment of spinal cord compression in lymphoma are important to avoid neurological disability.

**Key words:** Hodgkin's disease, pruritus, spinal cord compression.

Acta Med Scand 206 319-1979

Pruritus is a common systemic symptom in Hodgkin's disease (HD) and will disappear with successful treatment (3). We have observed a patient with severe pruritus associated with advanced disease, whose clinical signs of progressive disease unexpectedly accompanied by a reduction of pruritus. The relief of itching turned out to be an early sign of spinal cord compression due to an extradural manifestation of HD.

## CASE REPORT

The patient is a 33-year-old man with the nodular sclerosing type of HD, clinical stage IV, diagnosed in 1972. Initial treatment with the MOPP chemotherapeutic regimen was successful but since 1977 there have been progressive signs of HD despite several attempts to control the disease with various schedules of chemotherapy. Fever, weight loss and a severe generalized pruritus have been present for the last year. A destruction in his sternum was found in Oct. 1978 and at the same time a subcutaneous nodule in the thoracic wall became palpable. Fine needle

aspiration biopsies showed that the sternal and cutaneous lesions were caused by HD.

In Jan. 1979 pruritus in the trunk and lower extremities improved remarkably. However, the subcutaneous lesion was unchanged and the patient had persistent fever, night sweats and an elevated ESR, 60 mm/h, indicating persistent active disease. He also got pains between the shoulders and physical examination revealed an impaired sensibility for touch below the breast nipples. There was no impairment of motor functions and the tendon reflexes were normal.

Myelography revealed a spinal cord compression due to a left-sided lateral extradural tumour at the Th II level and radiation therapy was instituted. The pain between the shoulders disappeared after about 10 days. Pruritus returned concurrently in the trunk and legs and generalized pruritus again became a troublesome symptom.

## DISCUSSION

The disappearance of pruritus in our patient was obviously not due to a proper control of his disease by chemotherapy. On the contrary, the persistent cutaneous lesion, fever and elevated ESR indicated a considerable activity in his lymphoma. The most probable explanation of the relief of pruritus is that the compression of the spinal cord affected the spino-thalamic tracts known to transmit the itching impulses (2). The finding of a coexistent hypoaesthesia in the trunk and lower extremities is also compatible with an affection of the spino-thalamic tracts. Moreover, the pruritus returned following decompression of the spinal cord by radiation treatment of the extramedullary tumour mass.

The outcome of spinal cord compression in malignant lymphoma largely depends on the initial neurologic symptoms. When there are minor neurologic deficits, the chances of recovery following radiation therapy are good. The results of treatment become poorer when more advanced

neurologic symptoms with motor dysfunctions are present (1). Early diagnosis and treatment of spinal cord compression in patients with HD are therefore of utmost importance (3). In patients with signs of progressive disease and with systemic symptoms like fever and pruritus, a spontaneous relief of itching should evoke suspicion of spinal cord involvement and prompt a neurological examination.

Although the mechanisms bringing about pruritus in HD are still unknown (4), the relief of pruritus associated with spinal cord compression and the recurrent symptoms following treatment point to a peripheral origin of itching in HD.

## REFERENCES

- 1 Friedman M, Kim T H & Panahon. Cord compression in malignant lymphoma: incidence and results. *Cancer* 37: 1493, 1976.
- 2 Hassler R. The division of pain conditions into terms of pain sensation and pain awareness. Basic principles—pharmacology—therapy. Payne R & R A P Burt, p 98. Churchill Livingstone, London, 1972.
- 3 Peckham M J & McElwain T M. Complications. In Hodgkin's disease (ed D W Smithers) p 229. Churchill Livingstone, London, 1973.
- 4 Smithers D W. Skin involvement in Hodgkin's disease (ed D W Smithers) p 137. Churchill Livingstone, London, 1973.

# Isochromosome 17 in a Patient with a Myeloproliferative Disorder Terminating in Eosinophilic Leukemia

Bent Lonnqvist Gosta Gahrton Per Eriksson Kristina Friberg and Lore Zech

From the Department of Oncology and Hematology, the Department of Medicine, Huddinge Hospital, Huddinge, the Institute of Medical Cell Genetics, Karolinska Institute, Stockholm, and the Department of Medicine, Eskilstuna Hospital, Eskilstuna, Sweden

**CT** A patient is described who for more years had a myeloproliferative disorder terminated in eosinophilic leukemia. Chromosomes revealed an isochromosome 17 in all cells of bone marrow cells. This abnormality has been found in two out of six patients with leukemia investigated by banding technique and may therefore have etiologic importance. Some analysis in the hypereosinophilic syndrome has practical value for differentiating between malignant and non-malignant disease.

**Key words:** eosinophilic leukemia, isochromosome 17, cytogenetics.

Scand 206 371 1979

with eosinophilia, the peripheral blood film, and heart damage with no known cause for many years posed a difficult question: Is it a malignant or a non-malignant disease? Berglund (22) strongly doubted that eosinophilic leukemia existed. Bentley et al (2) tried to specify criteria for the diagnosis, while Anderson (15) preferred to talk about the eosinophilic syndrome. Some analysis may help to resolve this since the presence of a specific non-clonal chromosomal aberration in bone marrow is generally accepted as a sign of a pre-malignant cell clone. Before banding techniques were available, chromosome analyses in cases of eosinophilic leukemia had revealed Philadelphia chromosome (Ph) in some, but in most cases no consistent abnormalities. Only a few patients have been investigated with banding technique. This report describes a patient with a myeloproliferative disease

which terminated in a hyper-eosinophilic syndrome. Using the Q-banding technique, a consistent chromosomal abnormality was found in all bone marrow cells.

## PATIENT AND METHODS

### Patient history

The patient was a white male, born in 1906, who had been a foundry worker. Since 1973 he had had symptoms and signs thought to be caused by ischemic heart disease and easily managed with diuretics and nifedipine.

In July 1975, at a routine outpatient visit because of the heart complaint, a high Hb level (170 g/l) and an elevated WBC ( $18.4 \times 10^9/l$ ) were observed. Bone marrow aspirate on smears showed a normal amount of fat, thrombocytopoiesis and myelopoiesis were rather active and there was some eosinophilia. The patient felt well, there was no glandular hyperplasia, no hepatosplenomegaly, nor has there been any since then. In Feb. 1976 he was hospitalized in his home town because of gastric bleeding but felt otherwise well. In Sept. 1977, Hs Hb level was high (until then as a rule around 190 g/l) and WBC  $12.2 \times 10^9/l$ . Thrombocyte count was elevated with a highest recorded level of  $1317 \times 10^9/l$ . In Sept. 1975 the differential count showed 16% eosinophils, increasing to 40% one year later. Basophilic granulocytes were around 3% in those years. Four consecutive marrow aspirates showed less and less fat and more and more active proliferation of all cell lines (Tables I and II). The red cell volume was high, plasma volume normal and there were no signs of pulmonary disease. Polycythemia vera was strongly suspected and in Aug. 1977 he received 5 mCi  $^{32}P$ .

In Sept. 1977 the patient fell ill with a cough and a high spiking fever. X-ray showed extensive fast-changing pulmonary infiltrations. No infectious or parasitic disease could be diagnosed and his illness abated on 80 mg prednisolone daily. The pulmonary infiltrations disappeared. The muscular biopsy unfortunately not performed before the patient had received steroids did not show abnormal vessels. The Hb level fell and he needed transfusions. kept it at 80-100 g/l. Thrombocytes also fell to  $100 \times 10^9/l$ . They were of bizarre configuration.

Table I Hematological laboratory data (peripheral blood)

	Sept 1974	Nov 1975	March 1976	Dec 1976	Oct 1977	Nov 1977	Jan 1978
Hb (g/l)	190	190	132	190	95	92	89
Platelets ( $\times 10^9/l$ )	1 312	420	297	625	134	107	105
WBC ( $\times 10^9/l$ )	12.1	16.2	12.2	14.9	26.5	27.0	1
Eosinophils (%)	16	16	18	42	24	44	34

giant forms some were even larger than the eosinophilic granulocytes. The WBC climbed to around  $35 \times 10^9/l$  with 20–25% mature eosinophils, 6–7% basophils and 20–25% eosinophilic metamyelocytes and myelocytes. Less than 2% blastic cells appeared inconsistently in the differential count. The marrow displayed corresponding changes erythropoiesis and thrombopoiesis decreased the now massive cellularity was caused by increasing amounts of early eosinophilic cell forms which dominated the picture.

In Feb 1978 the patient was admitted to Huddinge Hospital for further diagnostic studies. Chromosome analysis was performed at this time (see below). The WBC on that day was  $28.6 \times 10^9/l$  with 55% eosinophilic granulocytes, one third of them being metamyelocytes and myelocytes. Platelet count was  $171 \times 10^9/l$ . Hb 81 g/l. Lysozyme in serum 12.6  $\mu g/ml$  (normal 5–10). Vitamin B<sub>12</sub> in serum 1140 pmol/l (normal 200–750). LAP index (patient score/control score  $\times 100$ ) 43.9 in blood 65.3 in marrow. Total heart volume was 890 ml corresponding to 580 ml/m<sup>2</sup> BSA. ECG showed sinus tachycardia and ST-T changes corresponding to the posterior wall of the left ventricle. ECG during exercise giving a pulse of 155/min showed no further changes. Two weeks later the patient developed a fast atrial fibrillation. Echocardiographic studies showed right ventricular hypertrophy confirmed by <sup>201</sup>thallium scintigram which also showed a defective uptake corresponding to the posterior wall of the left ventricle. Angiographic studies of abdominal arteries did not show the characteristic microaneurysmatic changes some times seen in periarteritis nodosa.

The disease was interpreted as. The patient was treated with busulfan for rod only due to lack of response and thrombocytopenia. Prednisolone 90 cristine 2 mg weekly kept the fever and infiltrations under control.

On March 9 1978 the patient died consistent with a cerebral thrombosis or hemorrhage and he died on March 11 1978 studies were not undertaken.

#### Cytogenetic analysis

Metaphases from bone marrow cells were prepared from fresh aspirates. Metaphases from cells were prepared after 7<sup>th</sup> h in a phytohemagglutinin. Staining was performed to the Q banding technique (6). Metaphases were photographed in a fluorescence microscope. Karyotypes were then prepared using conventional techniques.

## RESULTS

Twenty bone marrow metaphases were analyzed. All had an isochromosome 17 (Fig. 1) or extra chromosome no. 13. No other abnormalities were found. Six peripheral blood metaphases were also analyzed. All showed normal karyotypes.

Table II Bone marrow differential count (% cells)

	July 1974	Nov 1975	March 1976	Oct 1977	Nov 1977	Jan 1978
Neutrophilic cells (granulocytes + metamyelocytes + myelocytes)	40	50	41	21.4	71.5	19
Eosinophilic cells (granulocytes + myelocytes)	20	14	15.5	39.5	14.5	51
Promyelocytes	6	4.5	5.5	6.4	7.3	7
Myeloblasts	3	0.5	2	13	4	9
Red cell precursors	17	24	20.5	14.4	1	5
Other cell types	14	7	15.5	5	1.5	

\* Many pseudo-Pelger Huet cells and heavy toxic granulation.

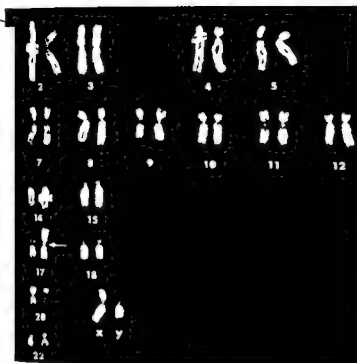


Fig 1 Karyotype from a bone marrow cell showing isochromosome 17 ( $\times 925$ )

# DISCUSSION

presented with a myeloproliferative kin to polycythemia vera. The disease ssed and acquired all the criteria of the ophilic syndrome  
above the nature of the hypereosino- rome has been much debated. Arguments ndrome including Löffler's endocarditis

parietalis fibroplastica is malignant are the frequently very poor prognosis and the heavy organ infiltration of eosinophilic cells. Many patients have other symptoms compatible with a premalignant or malignant myeloproliferative disorder such as erythrocytosis (16, 24, 26), myelofibrosis (3, 14, 23), high serum vitamin B<sub>12</sub> level (8, 11), high percentage of basophilic cells in the peripheral

## Chromosome analysis (Q banding or G banding) in six patients with eosinophilic leukemia

Dura- tion of disease (mo)	Myo- cardial involve- ment	Serum vitamin B <sub>12</sub>	LAP score	WBC ( $\times 10^9/l$ )	Eosino- phils (%)	No. of abnormal metaphases/ total meta- phases	Chromosomal abnormality	Ref
7	None	Normal	High	45.0	67	20/20	47XY +8	27
>7	None	High	Low	47.5	88	60/60	46XY iso- chromosome 17	21
6	Yes	Not re- ported	Not re- ported	300.0	80	31/37	47XY +10	13
3.5	Yes	Not re- ported	Low	33.0	65	42/43	49XYY t(3;5)+8 + marker	4
33	Yes	High	Low	22.6	55	Not re- ported	46XY short Y	10
33	Yes	High	Low	35.0	55	20/20	46XY iso- chromosome 17	Present study

blood (8-28) impaired eosinophilic maturation (5) and most important chromosomal aberrations in the bone marrow cells (5-8-27).

Before the banding technique became available Chusid et al (8) reported that 7 out of 13 investigated patients with the hypereosinophilic syndrome had abnormal karyotypes. One of these patients had a Ph<sup>1</sup> in all bone marrow metaphases and another six Ph<sup>1</sup> positive patients have been described (27). A case with a double Ph<sup>1</sup> has been reported recently (1). However there does not seem to be any record of the typical t(9;22) translocation in eosinophilic leukemia. Only 6 patients have so far been reported after investigation with banding techniques (Table III). Trisomy 8 trisomy 10 isochromosome 17 and a short Y chromosome are the abnormalities found. It is interesting that all these abnormalities have also been found in chronic myelocytic leukemia (7-9-12-19). With the exception of the Philadelphia chromosome they are generally found only shortly before or during blastic transformation. In rare cases trisomy 8 may also be found in a chronic stage of chronic myelocytic leukemia (18-19-20). These abnormalities may also occur in other myeloproliferative disorders (17). For example trisomy 8 is one of the most common aberrations in acute myeloblastic leukemia and is also found in polycythemia vera (25). Isochromosome 17 has also been demonstrated in other leukemias and lymphomas (4-18-25).

The spectrum of chromosomal abnormalities in patients with the hypereosinophilic syndrome clearly indicates that this disease includes a pre-malignant or malignant myeloproliferative disorder related to leukemia which could probably best be called eosinophilic leukemia. Whether the chromosomal abnormalities have the same prognostic implications as in chronic myelocytic leukemia is however uncertain. Although isochromosome 17 was found in our patient only about one month before death blast cells were not predominant. Unfortunately chromosomal analysis was not carried out early in the disease and therefore it is not known whether the patient had the abnormality already at its onset 3 years before death. In other patients (Table III) trisomy 8 trisomy 10 and isochromosome 17 were not reported to be associated with a rapid course of the disease. This agrees with our previous impression that the specific chromosomal disorders do not have the same prognostic implications in different variants of the syndrome.

## ACKNOWLEDGEMENTS

This work was supported by grants from the Cancer Society and the Swedish Social Sciences.

## REFERENCES

- 1 Allan N C, Duvall E & Stock J G. Chemotherapy for chronic granulocytosis. *Lancet* 1: 523 1978.
- 2 Bentley H P Jr, Reardon A E, Kave Krivit W. Eosinophilic leukemia. Report with review and classification. *Am J Med* 1961.
- 3 Benveniste D S & Ultmann J E. Leukemia. Report of five cases and literature. *Ann Intern Med* 71: 731 1969.
- 4 Bitran J D, Rowley J D, Flapp F M & Ultmann J E. Chromosomal abnormality in a patient with hypereosinophilic syndrome for a malignant disease. *Am J Med* 63: 1.
- 5 Brandt L, Mielman F, Beckman G & Nordenson I. Different composition of eosinophilic bone marrow pool in eosinophilia and eosinophilic leukaemia. *Acta Med Scand* 201: 177 1977.
- 6 Caspersson T, Lomakka G & Zerk. Fluorescence patterns of the human chromosomes—distinguishing characteristics. *Hereditas* 68: 89 1971.
- 7 Castleman B, Scully R E & McNee. Records of the Massachusetts General Hospital 18–1973. *N Engl J Med* 248: 957 1973.
- 8 Chusid M J, Dale D C, West B C M. The hypereosinophilic syndrome. *N Engl J Med* 1975.
- 9 First International Workshop on Chronic Leukaemia. Chromosomes in Philadelphia positive granulocytic leukaemia. *Br J Haematol* 47: 1.
- 10 Flannery E P, Dillon D E, Freeman Levy J D, D'Ambrosio U & Boffi. Eosinophilic leukemia with fibrosing end-stage short Y chromosomes. *Ann Intern Med* 77: 1.
- 11 Fledelius H. Extreme persistent eosinophilia with high serum B12 values. A report of two cases. *Med Scand* 187: 235 1970.
- 12 Gahrton G, Lindsten J & Zerk. Leukemia of chromosomes 8-9-19 and 22 in Philadelphia negative chronic myelocytic leukemia in chronic or blastic stage. *Acta Med Scand* 196: 351.
- 13 Goldman J M, Najfeld V & Theng. Cytogenetic and chromosome analysis of leukemia. *J Clin Pathol* 28: 946 1974.
- 14 Grant M D, Horowitz H I, Luzzo & Spiegelvogel A R. Eosinophilic leukemia with acute blastic transformation of a case with review of literature. *Cancer* 1974.
- 15 Hardy W R & Anderson R E. The hypereosinophilic syndrome. *Ann Intern Med* 68: 1.
- 16 Hay J & Evans W H A. Eosinophilic leukaemia and eosinophilia erythrocytic. *Med* 22: 167 1929.

- J Gahrton G, Lindsen J, Simonsson C & Zech L. Trisomy 8 in acute leukemia and secondary chronic anemia. *Br J Haematol* 1974
- D Chromosomes in haematology. *Br J Haematol* 1977
- J S Porter A M, Watmore A E, Sokol R J & Wood J K. Myeloid and the malignant phase of chronic leukaemia. *Br J Haematol* 39 117 1978
- R Gahrton G, Friberg K & Zech L. In the chronic phase of Philadelphia negative myelocytic leukaemia. *Scand J Haematol* 1978
- F Panan A & Brandt L. Isochromosome case of eosinophilic leukaemia. *Scand J Haematol* 1978
- 3 Eosinophilic leukemia and disseminated eosinophilic collagen disease—a disease entity? *Acta Med Scand* 177 179 1965
- 73 von Papageorgiou A. Zur Differenzialdiagnose der eosinophilen Leukämie. *Blut* 8 338 1967
- 74 Rosenthal D S & Moloney W C. Occurrence of acute leukaemia in myeloproliferative disorders. *Br J Haematol* 36 373 1977
- 25 Rowley J D. The role of cytogenetics in hematology. *Blood* 48 1 1976
- 76 Thomas J E. Eosinophilic leukemia presenting with erythrocytosis. *Blood* 22 639 1963
- 77 Wenzel A, Westin J & Swolin B. Philadelphia negative eosinophilic leukaemia with trisomy 8. Case report and review of cytogenetic studies. *Scand J Haematol* 18 413 1977
- 78 Yam I T, Li C Y, Necheles T F & Katayama I. Pseudo-eosinophilia: eosinophilic endocarditis and eosinophilic leukemia. *Am J Med* 53 193 1977





# Isovolemic Hemodilution in Erythrocytosis Secondary to Chronic Obstructive Lung Disease

Mats Danielson and Jorgen Nordenstrom

From Medical Department VI Södersjukhuset, Stockholm, Sweden

**ACT** Patients with chronic obstructive lung disease present with a combination of respiratory and circulatory insufficiency. In secondary erythrocytosis (polycythemia) blood viscosity rises and impairs peripheral oxygenation. Against this background a patient with acute exacerbation of a respiratory disease with secondary erythrocytosis was treated with isovolemic hemodilution in two periods of hospitalization. During each of these periods hemodilution was achieved by removing 1700 and 1700 ml blood, respectively, and this simultaneously by infusing equal volume of dextran 70 (Macrodex<sup>®</sup>). The patient's general condition improved, her dependence on supplementary oxygen drastically decreased, and the hematocrit values improved after hemodilution. The course of the disease in this case suggests that the erythrocytosis rather than hypervolemia contributed to the patient's poor condition. It also indicates that intensive diuretic therapy in cardiac failure with concomitant erythrocytosis can improve the hemocirculation and thereby add to the treatment of an already overloaded circulation.

**Key words:** hemodilution, lung diseases—obstructive, erythrocytosis.  
Acta Med Scand 206 327-1979

Respiratory insufficiency is a very serious condition for the patient, exceptionally distressing condition. Conventional means of treatment seldom result in a clearly marked improvement and in non-emergency cases respirator treatment is hardly practical. In chronic obstructive lung disease with secondary erythrocytosis, impaired central and peripheral circulation can contribute to impaired tissue oxygenation. In such cases hemodilution can be a useful supplement to conventional therapy.

## THE PATIENT AND METHODS

The patient was a 67-year-old woman with symptoms of chronic bronchitis for 20 years. She used to be a heavy

smoker but in recent years her cigarette consumption had been about 10 per day. Breathing difficulties had increased over the last four years and the least exertion resulted in considerable breathlessness. Since 1973 she had had oxygen at home and generally had to use it several times a day. She had been admitted to the hospital on several occasions during the last 3 years because of acute exacerbation of breathing distress. On these occasions blood gas analyses revealed hypoxemia, hypercapnia and a compensated respiratory acidosis. Spirometry showed considerably obstructed ventilation. Blood tests showed erythrocytosis. There was no deficiency of  $\alpha_1$ -antitrypsin. For many years the patient had been treated with  $\beta$ -adrenergic receptor stimulants, theophylline preparations, expectorants and in certain periods corticosteroids and broad spectrum antibiotics. In addition she has been on digitalis and diuretics for a long time.

The description below refers to the progress of the disease during two periods of hospitalization (March and Oct. 1977) when the patient's acute stages of respiratory and circulatory insufficiency were treated by isovolemic hemodilution. On both occasions the patient was dyspnoic, darkly cyanotic and in very poor general condition on admission. There were no signs or symptoms of infection. On the second hospitalization there was slight ankle edema, slight dilatation of the pulmonary vessels detected by radiography, but the size of the heart was within normal limits.

During the first stay in hospital the patient was treated with breathing physiotherapy, salbutamol 4 mg  $\times$  4, proxiphyllin 0.4 mg  $\times$  3, ACTH injections (max. 60 IU  $\times$  4), digtoxin tabs 0.1 mg  $\times$  1, expectorant and when necessary proxiphyllin 0.1 g/ml 4 ml i.v. and adrenaline 1 mg/ml 0.5 ml s.c. In addition she received oxygen via nasal catheter to meet subjective requirements, which initially meant almost continuous oxygen administration. This therapy was administered for 6 days without any change in her general condition. In order to reduce the pronounced tissue hypoxia, hemodilution was initiated on the seventh day and carried out over a period of two weeks, whereby a total of 1700 ml venous blood (5  $\times$  300-500 ml) was removed and immediately replaced by the same volume of dextran 70 (Macrodex<sup>®</sup>).

During the second hospitalization initial treatment was the same as during the first. Two days after admission the patient received i.v. injections of furosemide (Lasix<sup>®</sup>) 40 mg  $\times$  3 and proxiphyllin (Theon<sup>®</sup>) 4 ml  $\times$  4 for four days because of increasing difficulty in breathing, with signs of cardiac compensation.

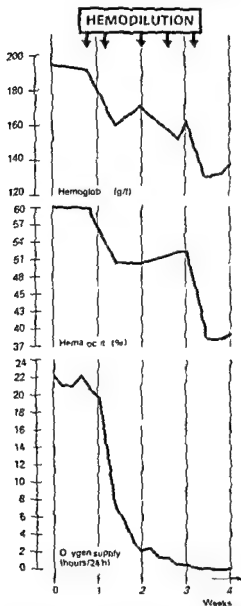


Fig. 1 Effect of hemodilution on Hb concentration, Hct and oxygen administration during the first hospitalization.

As the patient's condition successively deteriorated over the following weeks, isovolemic hemodilution was again carried out. This time a total of 1750 ml blood was removed and simultaneously replaced by dextran 70 infusions on five occasions.

## RESULTS

During the first stay in hospital the patient received traditional treatment for respiratory distress for six days without improvement. After hemodilution Hb and Hct decreased, the dependence on supplementary oxygen diminished and the oxygen

Table 1 Blood gas values with and without supplementary oxygen during the first period before and after hemodilution

	Before	
	With out O <sub>2</sub>	With O <sub>2</sub>
aB-pH (U)	7.40	7.39
aB-CO <sub>2</sub> (kPa)	8.4	7.7
B-standard bicarbonate (mmol/l)	35	35
aB-base excess (mmol/l)	+12	+8
aB-O <sub>2</sub> (kPa)	4.0	4
aB-O <sub>2</sub> saturation (%)	60	68

administration could be successively reduced. In spite of this the blood gas values (Table 1). Spirometry values were normal and unchanged after hemodilution with obstructed and restricted ventilation:  $\dot{V}_E$  16 l (30), residual volume 4 l (1.5) FEV<sub>1</sub> (2.2) FEV<sub>25</sub> 31% (70) MVV<sub>25</sub> 15 L/min (33). (Normal values are given in parentheses).

During the first two weeks of the second stay, conventional treatment of the respiratory cardiac insufficiency gave no improvement; contrary, the patient's condition continued to deteriorate with both clinical and radiological signs of increasing cardiac insufficiency. Institution of hemodilution, her general condition rapidly improved and the cardiac symptoms regressed. The patient's Hb concentration, blood gases during the second stay in bed are presented in Fig. 2. It is important to note that samples for blood gas analyses taken during the period of oxygen therapy were drawn when oxygen was being administered, whereas samples taken during the hemodilution period were taken when oxygen was not being administered. The improvement in blood gas values after hemodilution was thus better than that presented in Fig. 1. It is evident from Fig. 2 that Hb and Hct rose at the beginning of hospitalization. This hemoconcentration coincides with the institution of diuretic therapy, 240 mg furosemide daily, which was prescribed in order to reduce pulmonary congestion. Hct thus rose from 35% to a maximum of 67%. The patient's blood gas values successively deteriorated at the beginning of hospitalization and at worst pO<sub>2</sub> was 3.9 kPa and

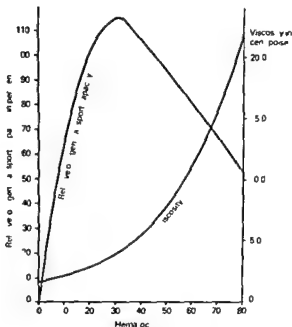
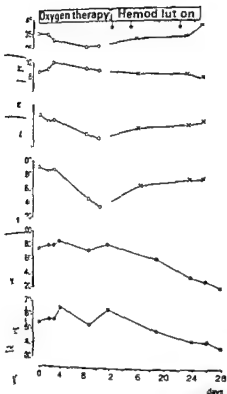


Fig. 3. Relationship between Hct, relative oxygen transport capacity and blood viscosity (Aster Hent (11)).

blood gases, Hb concentration and Hct during hospitalization. O = Oxygen was being administered when blood gas samples were taken. X = no Oxygen was administered at the time of

hospitalization was 33% despite continued administration. Blood gas values only improved when solvent hemodilution was performed. From Fig. 2 the Hb and Hct were mirror images of the  $pO_2$  and  $O_2$  saturation. The most serious blood gas disturbance occurring when Hct was highest. Hct returned to normal after hemodilution, while blood gases approached normal. Thus, after both of hospitalization the patient could be considered in good condition. During the intervening 18 months she felt in better condition than in previous years except for the few weeks immediately prior to readmission.

## DISCUSSION

Chronic obstructive lung disease often results from a combination of respiratory and circulatory insufficiency. The respiratory insufficiency is mainly due to insufficient alveolar ventilation

in relation to the production of carbon dioxide and this leads to chronic hypoxemia and hypercapnia (4). These chronic changes in the blood gases cause a number of hemodynamic disturbances at both central and peripheral levels. Thus in advanced cases an increase may occur in pulmonary vascular resistance, pulmonary hypertension, right chamber insufficiency, hypervolemia and secondary erythrocytosis with raised blood viscosity (16, 20, 23).

Hypervolemia commonly occurs in chronic obstructive lung disease (10). The importance of hypervolemia in the etiology of pulmonary hypertension is not yet clear. Certain authors consider that hypervolemia is of little or no importance in this situation since no reduction of pulmonary arterial pressure has been noted after the reduction of blood volume (1, 2). Gertz (8) however considers that hypervolemia contributes to the development of pulmonary hypertension and hypoxemia and therefore recommends long term treatment with diuretics in order to maintain a normal blood volume.

Patients with chronic obstructive lung disease show much the same erythropoietic response to chronic hypoxia as normal persons (23). The fact that man has erythrocytosis is relatively unusual in

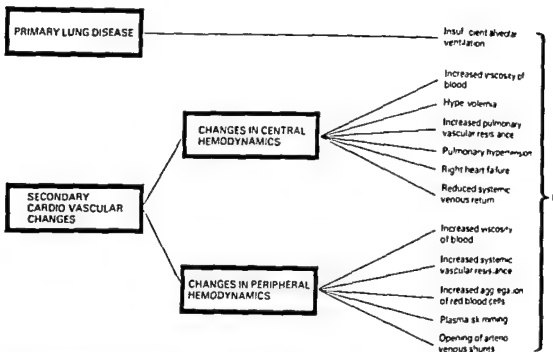


Fig 4 Schematic representation of factors contributing to hypoxia in chronic obstructive lung disease with secondary erythrocytosis

hypoxic lung disease has been ascribed to suppression of bone marrow by hypercapnia and to repeated airway infections (20). Also an increased plasma volume will give a normal Hct value in spite of secondary erythrocytosis (20). In acute exacerbations of respiratory insufficiency, nutrient and fluid intake are often reduced and this can cause a hidden erythrocytosis to become overt.

In secondary erythrocytosis with raised Hct, the viscosity of blood is also raised, which can lead to peripheral resistance, reduced capillary flow, reduced venous return and reduced cardiac output (13). In addition, the viscosity of blood rises exponentially with rising Hct (Fig. 3) (11). Karp et al. (12) found that pulmonary vascular resistance increased proportionally with increasing Hct and considered viscosity to be an important factor in pulmonary vascular resistance. Within the microcirculation, erythrocytosis and hemoconcentration increase the tendency for red blood cells to aggregate, which together with the raised viscosity leads to sluggish blood flow and impaired oxygen supply to the tissues (15). Plasma skimming and opening of arteriovenous shunts are other phenomena which occur in erythrocytosis and contribute to tissue hypoxia (7). Hypoxia thus has a

multifactorial etiology in advanced chronic obstructive lung disease and can be attributed partly to primary lung disease and partly to the central and peripheral hemodynamic changes (Fig. 4).

Hemodilution (exchange transfusion) is utilized to break this vicious circle of respiratory and circulatory disturbances. Hemodilution means that the blood is diluted by removing a certain volume of blood and simultaneously infusing an equal volume of an osmotically active solution. In order to maintain isovolemia in the patient, colloid solutions such as dextran 40 must be used (22). The reduction of Hct by hemodilution reduces blood viscosity and peripheral resistance and increases venous return and cardiac output. These effects result in improved capillary perfusion and oxygen transport. It is the fact that hemodilution reduces the concentration of oxygen-bearing components (red blood cells) increased peripheral oxygenation is achieved because of the improvement in microcirculation (11). For rheological reasons, the oxygen transport capacity of blood is greatest at a Hct around 30%, i.e. somewhat lower than normal (13). This has been theoretically calculated to be

confirmed by animal experiments and studies in man (14-15).  
 The treatment of erythrocytosis is venesection procedure however has not been shown long term effect on blood gases or haemodynamics. Only a short acting transective effect has been observed (5-19).  
 Hemodilution has been recommended. A reduction of the red cell volume (18) can be drastically reduced by this. Gregory (9) reported that up to 3500 ml could be exchanged without injury to the patient. He has performed hemodilution with 40 patients with erythrocytosis, corresponding peripheral arterial insufficiency with anginal attacks.  
 In the case of cardiac insufficiency and erythrocytosis simultaneously it should be borne in mind that although diuretics admittedly reduce plasma volume they leave the red cell volume unchanged. This causes an already raised Hct to rise which leads to a further increase in blood viscosity and worsened peripheral circulation with tissue hypoxia (17). This phenomenon occurred in our patient during her second period. The fact that her condition deteriorated after therapy but improved after isovolemic exchange suggests that a raised red cell volume caused a raised blood volume was responsible for the particular patient's poor condition.  
 Iron is excreted via the kidneys to a lesser extent in dextran 40 and remains longer in the circulation. Since our primary intention was to reduce the raised Hct we used dextran 70 (Macrodex) which is a superior plasma expander in the treatment of hemodilution in a patient with acute respiratory distress because of chronic bronchitis. Secondary erythrocytosis has on two occasions caused an expected fatal outcome. Since the prognosis is severe in chronic obstructive lung disease a prognosis comparable to that in heart disease (3) one should utilize every possible symptomatic improvement. With this association we wish to point out the value of hemodilution as a supplementary form of therapy when respiratory and circulatory insufficiency co-exist.

## REFERENCES

1. A. S. Cole, M. D. Green, I. D. North, W. H. R. B. Clarke, S. W. & B. Shop J
2. Factors contributing to the reversible pulmonary hypertension of patients with acute respiratory failure studied by serial observations during recovery. *Circ Res* 74:51 1969
3. Bishop J. M. The origins of pulmonary hypertension in patients with chronic bronchitis and emphysema. Form and function in the human lung (ed. G. Gammans & L. B. Hunt) pp 134-145. Livingstone Edinburgh and London 1968
4. Burrows B. & Earle R. H. Course and prognosis of chronic obstructive lung disease. *N Engl J Med* 780:397 1969
5. Cherniack R. M. The management of acute respiratory failure. *Chest* 58:477 1970
6. Dayton L. M., McCullough R. E., Scheinhorn D. J. & Weil J. W. Symptomatic and pulmonary response to acute phlebotomy in secondary polycythemia. *Chest* 6:785 1975
7. Gelin L. E. Disturbance of the flow properties of blood and its counteraction in surgery. *Acta Chir Scand* 177:787 1961
8. Gelin L. E. & Ingelman B. Rheomacrodex—a new dextran solution for rheological treatment of impaired capillary flow. *Acta Chir Scand* 122:794 1961
9. Gertz I. Management of acute respiratory failure in chronic obstructive lung disease. Dissertation Karolinska Institutet Stockholm 1976
10. Gregory R. J. The rapid lowering of hematocrit by exchange transfusion of Rheomacrodex dextran 40. *Acta Med Scand* 189:551 1971
11. Harvey R. M., Ferrer M. J., Richards D. M. & Courmand A. Influence of chronic pulmonary disease on the heart and circulation. *Am J Med* 10:719 1951
12. Hint H. The pharmacology of dextran and the physiological background for the clinical use of Rheomacrodex and Macrodex. *Acta Anaesthesiol Belg* 2:119 1968
13. Karp R. B., Nadel J. A., Graf P. D. & Murray J. E. Effects of perfusable viscosity on pressure flow relationship and vascular resistance in the dog. *J Clin Invest* 46:1976 1967
14. Klovekorn W. P., Pichler H., Ott E., Bauer H., Sunder-Plassman L., Jesch F. & Messmer K. Acute preoperative hemodilution in surgical patients. *Br J Haematol* 41:748 1975
15. Laks H., O'Connor N. E., Pilon R. N., Andersson W., MacCallum J. R., Klovekorn W. P. & Moore F. D. Acute normovolemic hemodilution: Effects on hemodynamic oxygen transport and lung water in anesthetized man. *Surg Forum* 24:701 1973
16. Messmer K. & Sunder-Plassman L. Hemodilution. *Progr Surg* 13:708 1974
17. Replogue R. L. & Merrill E. W. Experimental polycythemia and hemodilution. *J Thorac Cardiovasc Surg* 60:587 1970
18. Saumarez R. C. & Gregory R. J. Exchange transfusion in polycythemia. Intentional hemodilution. *Br J Haematol* 41:278 1975
19. Schaannig J. & Sparr S. Bloodletting and exchange transfusion with dextran 40 in polycythemia secondary to chronic obstructive lung disease. *Scand J Resp Dis* 55:237 1974

- 19 Segel N & Bishop J M The circulation in patients with chronic bronchitis and emphysema at rest and during exercise with special reference to the influence of changes in blood viscosity and blood volume on the pulmonary circulation *J Clin Invest* 45 1555 1966
- 20 Shaw D B & Simpson T Polycythemia in emphysema *Q J Med New Series* XXX 118 135 1961
- 21 Sluiter H J Blokzijl E J van Dijk W Heeringen J R Hilvering C & Steenhuis E J Conservative and respirator treatment of acute respiratory insufficiency in patients with chronic obstructive disease *Ann Rev Respir Dis* 104 919 1972
- 22 Sinder Plassman L Klövekom W P N & Messmer K The dynamics of the fluid balance as affected by colloid water *Surg Res* 4 354 1972
- 23 Vanier T Duffano J M Clyde W & De F Emphysema hypoxia and the polychromatophane response *N Engl J Med* 269 169 1963

## LETTERS TO THE EDITOR

# PROPRANOLOL FOR THE TREATMENT OF HYPERTENSION IN PREGNANCY

It is known that 40-60% of British obstetricians consider the presence of hypertension in pregnancy (1). As a similar development probably in Scandinavia. I find it important to state that this treatment is still controversial. Propranolol decreases cardiac output and increases peripheral resistance with a resultant reduction in intracranial pressure including probably the uterus and the vasoconstrictor effect must be considered. Furthermore, because vasoconstriction is an essential feature in severe preeclampsia and eclampsia. Moreover propranolol crosses the placenta and may harm the foetus.

Some reports have suggested a causality between fetal treatment and placental insufficiency and fetal tachycardic response to hypoxaemia and hypotension at birth and hypoglycaemia and hypothermia during the neonatal period. There have been no reports of congenital malformation related to propranolol.

There is a well known series of 20, 10, 76 and 9 cases have been published all indicating no maternal or fetal complications of propranolol treatment (2). Recently a series of 24 pregnancies (propranolol treatment 9, other antihypertensive treatment 15) has indicated a poor foetal prognosis associated with propranolol treatment (4). The stimulating effect of propranolol on uterine tone does not seem to be a significant factor in practical obstetrics.

Even if treatment is perhaps really harmless during pregnancy and complications may be rare but larger prospective investigations to confirm this are necessary. At present consequently propranolol should not be used routinely during pregnancy. If used the treatment should be given with increased caution.

From the Department of Medicine, Hørsholm Hospital, Denmark.

## REFERENCES

1. Lieberman G, V P, Lewis P J, DeSwiet M & Pitt C J. How obstetricians manage hypertension in pregnancy. *Br Med J* 1 626 1978.
2. Kihou H, E, Silverberg D, S, Resn E, Romen M, Shih S & Serr D M. Propranolol for the treatment of hypertension in pregnancy. *Br J Obstet Gynaecol* 85 431 1978.

3. Goodwin J F & Oakley C M. The cardiomyopathies. *Br Heart J* 34 545 1972.
4. Lieberman B A, Stratton G M, Cohen S L, Beal R W, Pinner G D & Belsey E. The possible adverse effect of propranolol on the fetus in pregnancy complicated by severe hypertension. *Br J Obstet Gynaecol* 85 678 1978.
5. Tcherdakoff Ph, Collard M, Berrard E & Kref C. Propranolol in hypertension during pregnancy. *Br Med J* 7 670 1978.
6. Tcherdakoff Ph & Kref C. Traitement par le propranolol de l'hypertension artérielle chez la femme enceinte. *Nouv Presse Med* 6 679 1977.

## ELECTRICAL ALTERNANS

Sir

We would like to comment on a recent case report of phasic voltage alternation in spontaneous left-sided pneumothorax (1).

We have recently seen a similar case in a 51-year-old man who presented to our Out Patient Department. Three weeks previously he had developed a sudden onset of left-sided chest pain associated with moderate dyspnoea. This was initially resolved but he continued to notice occasional left-sided chest pain and mild dyspnoea on exertion over the next three weeks. Physical examination revealed the signs of a left-sided pneumothorax and chest radiograph confirmed this with the pneumothorax occupying approximately 50% of the lung field.

An ECG showed phasic voltage alternation on several leads (Fig. 1). We would like to suggest that despite the apparent lack of case reports in the world literature phasic voltage alternation may occur more commonly than is recognised in left-sided pneumothorax. This may not be detected for the simple reason that ECGs are rarely performed in these patients.

Similarly we would like to challenge the suggestion that the ECG is a useful diagnostic tool in the diagnosis of pneumothorax since electrical alternans may occur in pericardial effusion (?). Pneumothorax surely remains the impenetrable domain of the chest radiograph.

Yours sincerely

M. Arthur S. P. Hanley and A. Clark  
Department of Medicine, General Hospital  
Park Row, Nottingham, England

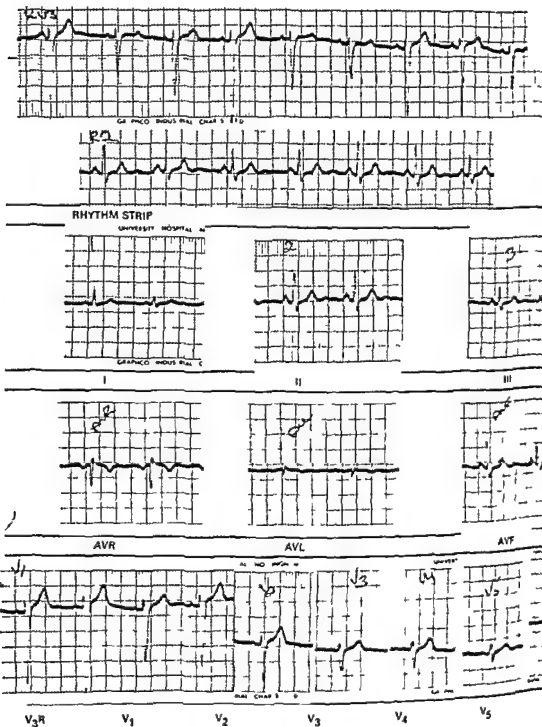
## REFERENCES

1. Hallengren B. Phasic voltage alternation in spontaneous left-sided pneumothorax. *Acta Med Scand* 205 143 1979.
2. Kleinfeld M, Steiner E & Kossman C. *Am Heart J* 65 495 1963.





Fig 1 ECG showing phasic voltage alternation



agree with Dr Arthur and colleagues that this information may well be very common in left-sided thorax. A larger series would, however, be necessary to establish the frequency.

As to our experience: ECG is frequently performed in patients with left-sided chest symptoms. This is why ECG is a useful diagnostic tool in thorax—the ECG may demonstrate typical

changes indicating the correct diagnosis which can subsequently be verified radiologically. However, we do not claim that the diagnosis can be made exclusively electrocardiographically.

Yours sincerely

Bengt Hallensjö

Department of Medicine, University of Lund  
Malmö General Hospital, Malmö, Sweden

## BOOK REVIEWS

*Endocrine System*, 3rd revised edition. Edited by Labhart. 1079 pages, 411 illustrations, 35 tables. \$108.90. Springer Verlag (ISBN 3 540-36100 0). Heidelberg and New York, 1978.

For several years, this has been the leading endocrinology in Continental Europe. This current and third edition has been considerably enlarged, and the number of authors who have been invited to write certain chapters is considerable. Not only is the number but the quality of the contributions. Labhart has succeeded in keeping the composition of the book very homogeneous and as a result, he himself the author of many chapters. This non-est-d-sputandum is an old and widely expressed opinion. The editor would be inclined to rule by saying that endocrinology is the flower of medicine. No other branch of our science deals with Wirkstoffe, active substances that are endocrine and therefore not foreign to the patient's organism in the widest sense of the word—and they are included in that sense by Labhart—are of course the therapeutic agents as they are self-made. Nothing is more satisfying than the substitution of a lacking book that helps us to discuss such problems in a central place in the library of every physician.

There are many great qualities in this volume. Being a first edition, it should say that the emphasis on individuality is exemplified by a large gallery of patient pictures. One of the many excellent features of this volume is that the authors draw from a wide and well-founded personal experience. In many instances, the anecdotal is important, and that the anecdotal is important than large materials treated statistically. It is enlivened with some modern biochemical and physical methods. The single patient judged by the observer is still the basis of clinical medicine. This volume teaches us important lessons in

science, but this is also more or less a matter of taste. On the whole, it is unusual to find a textbook that quotes studies from countries with many different languages. Also, in this respect, it represents the best Swiss tradition. The endocrinologist who is not a professional endocrinologist will note, with great satisfaction, that so-called tissue hormones and also the new family of neurohormones, by many regarded as neurological transmitters, have been treated extensively. The chapters on the hypothalamus, the gut, and the pancreas contain excellent presentations from these fields. Also, the introductory chapters on hormone action are very well integrated into the general presentation, even if in a way they belong to general physiology.

The book is highly recommended, even if the price makes it inaccessible to many physicians' private libraries.

Jan G. Waldenström

*Current topics in hematology*, vol. 1. Edited by Sergio Pomelli and Stanley Yachin. 247 pages. \$24.00. Alan R. Liss, New York, 1978.

This is the first volume in a new series. It may well be that some colleagues are of the opinion that such progress reports in haematology have become too many. On the other hand, the subjects treated in this volume and many of those planned for future volumes are of general interest to a large number of members of the medical profession at large.

This volume treats several important topics in haematology, such as G6PD, haemoglobin, chelation therapy, hemochromatosis, and red cell shape. The pediatrician will also find a short but concentrated discussion on the special characteristics of the red cell in the newborn. The most extensive chapter has Luzzatto as one of the authors. He is one of the world authorities on problems related to disturbances of glucose-6-phosphate dehydrogenase and the treatment of the subject is excellent. Not only are biochemical problems connected with the cause and effect of mutations in the gene that codes for

recent advances have been included. The references are remarkably complete, and works from European and American institutions have been quoted. It is easy to find individual papers that are missing in the central position in scientific discussions.

this enzyme discussed extensively. Also the epidemiology in the widest sense of the word is treated with the aid of very interesting maps of the world. The fact that G6PD—next to globin—is the most heterogenous protein molecule that we know of leads to many interesting hypotheses. It could well be that these genes are really hypermutable. It could also be that small differences are easy to detect. In both instances such changes have led to differences in electrophoretic mobility. The third could be that such small changes are well tolerated or even have a selective advantage. It is now a dogma that the last assumption is

true—but nothing contradicts the hypothesis. Genes may be less stable, i.e. hypermutable. It can be assumed that most G6PD variants are of single site mutations just like haemoglobin.

The volume can be recommended to the interest in haematological problems. Also one will find a well written paper on the enzyme in human neonate.

J. L. G. M.

## ANNOUNCEMENT

*The seventh annual meeting of The International Society for the Study of the Lumbar Spine* will be held in New Orleans, Louisiana, USA, May 24–28, 1980 for members and invited guests.

Non members wishing to submit papers for the program

should communicate with the secretary, Dr. Sunnybrook Medical Centre, 7075 Bayview Avenue, Toronto, Ontario, Canada M2N 3M5. Deadlines: 15 Jan. 1980.

## Stroke Registration in Goteborg, Sweden, 1970-75

## Incidence and Fatality Rates

Per Harmsen Goran Berglund Owe Larsson Gosta Tibblin  
and Lars Wilhelmssen

From the Departments of Neurology and Medicine I, Sahlgrenska Hospital and Ostra Hospital  
University of Goteborg, Goteborg, Sweden

ACT Strokes occurring among persons between 15 and 65 years of age (population 300 000) registered since 1970 in Goteborg, Sweden. The validity showed that less than 10% of strokes were undetected. During the period 1970-May 13, 1975, 986 stroke events occurred in 941 patients giving an annual average incidence rate of 73 (89 for men and 58 for women) per 100 000 individuals 15-65 years of age. The incidence rate for all ages was estimated to be about 200. The rates were higher for men than for women in all age groups. There was a female preponderance for subarachnoid haemorrhage but a male preponderance for other types of stroke. Incidence rates increased with age, most rapidly for cerebral and unspecified stroke. Fatality rates within 3 weeks after onset of stroke, they were higher for subarachnoid and intracerebral haemorrhage than for cerebral infarction and unspecified stroke. Incidence rates were lower than those found in similar studies from Denmark and Finland, but greater variations were found with respect to stroke fatality rates were similar to those found by other authors.

Stroke incidence, fatality rate, type of stroke  
Acta Med Scand 206 337-344 1979

Cerebrovascular disease is the second most common non-infectious cause of death in Sweden (17) and in other countries. Often it is responsible for disability in survivors. Cerebrovascular disease as a public health problem was recognized at the WHO meeting in Monaco in 1971 (19) and the need for reliable and comprehensive information on the incidence, course and prognosis of stroke in different communities was stated. The establishment of uniform registers of stroke patients is recommended (a) to provide information for

epidemiological studies on a community basis concerning natural history in clinical terms and in terms of impact on the public health system and (b) to evaluate intervention measures such as 1) primary and secondary prevention, 2) altered care in the acute stage of stroke and 3) rehabilitation.

During 1971-75 18 stroke registers were established under the auspices of the WHO in various parts of the world. Some results from these have been reported (1-10, 14). Goteborg was one of the communities in which stroke registration was started. This paper presents data on incidence and fatality in 986 cases of stroke occurring in the city of Goteborg during a 4½ year period from Nov. 1970 onwards.

## BACKGROUND

In recent years programmes for the study and control of cardiovascular diseases have successively been implemented in Goteborg. The emphasis is on ischaemic heart disease and hypertension. The programmes include prospective population studies (2, 15), a primary preventive trial (18) and secondary preventive trials in patients with myocardial infarction (7). As an underlying instrument of measurement, a Myocardial Infarction Register has been in operation since 1968 (6). In 1970 the programme was extended to include registration of cases of stroke occurring in the community.

**Location of study.** Goteborg, the second largest city in Sweden, is mainly an industrial and commercial centre. It is situated on the west coast and the climate is typically coastal with moderate differences between summer and winter.

**Population.** The total population of the city of Goteborg was 450 860 in 1970 and 445 704 in 1974. In 1970 13% and in 1974 15% of the inhabitants were aged 65 years and over. In 1970 8% of the population were aliens (41% Finnish).

**Organization of medical care.** Sahlgrenska Hospital (2500 beds) dominated medical somatic care in the city until Dec. 1977 and almost all patients with acute diseases

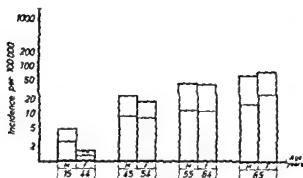


Fig 2 Intracerebral haemorrhage. Age and sex specific incidence and mortality (hatched areas) semilogarithmic scale

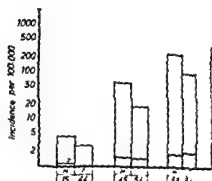


Fig 3 Cerebral infarction and unspecified. Age and sex specific incidence and mortality (hatched areas) semilogarithmic scale

mation on disease manifestations was derived from sources other than the Stroke Register but the Register had been used for checking the diagnosis.

**The study of women in Göteborg (2).** A representative sample of women aged 38–60 years ( $n=1462$ ) resident in Göteborg were examined during 1968–69 and 1974–75. Five cases of stroke were reported among them after 1970 and all had been entered in the Register.

**The primary preventive trial (18).** One third of all male residents of Göteborg, aged 47–54 years ( $n=7454$ ) were screened during 1970–73 and rescreened 4 years later during 1974–77. By 1976, 34 cases of stroke had been reported by participants since 1970. When checking with the patients or examining their case histories, 18 of these men did not fulfil the criteria for entry in the Stroke Register while 15 had been registered as stroke cases and one patient with stroke fulfilling the criteria had not been registered. An approximate detection rate of 15 (94%) out of 16 cases of stroke in this population was thus indicated.

**The Tynered project (16).** All visits to general practitioners in a defined district of Göteborg were recorded and coded according to diagnosis during 1974–76. The diagnosis of cerebrovascular disease (ICD code 430–438) accounted for 12 consultations by six patients aged below 65 years during this period. Their case histories were examined and in none of these cases had a stroke occurred after Nov. 1970 according to our criteria. Thus, no lapse in register coverage could be demonstrated in this way.

**Screening of 70 year old people in Göteborg (112).** One third of all residents of the city aged 70 years were

screened in 1971–72. During 1973, some 1000 persons were questioned concerning stroke by physician's interview. Thirteen gave a positive answer and seven of these said they were admitted to hospital at the time of the stroke. This is a lower figure than expected for hospital admission of stroke cases. These figures are uncertain, however, as the diagnosis was not further verified in these cases and the age group was older than that of the present study.

## RESULTS

During the period Nov. 15, 1970–May 1, 1973, 161 cases of stroke occurred in 941 patients, 15 years resident in Göteborg. The annual incidence rate (attack rate per 100,000 individuals aged 15–65 years) was 73 (89 for men, 58 for women). This difference is significant ( $p<0.001$ ). If only first strokes are considered, the incidence rate was 65 (77 for men, 53 for women).

The number of stroke cases and mortality rates by age group and sex are shown in Table IV. Mortality rates were higher for males than for females in all age groups.

The incidence rates for each type of stroke

Table IV. Number of cases of stroke and accumulated case fatality rates (FR %) in Göteborg

	No. of stroke cases	Dead at 3 weeks		Dead at 1 year		Dead at 2 years*	
		No.	FR	No.	FR	No.	FR
Males	602	147	24	193	32	57	46
Females	348	131	35	161	42	44	47
Total	986	280	29	354	36	101	47

\* 216 cases with onset of stroke in 1971 were followed for 2 years.

Number of cases of stroke and fatality rates (FR %) at 3 weeks by age group and type of stroke in 1970-75

Subarachnoid haemorrhage		Intracerebral haemorrhage		Cerebral infarction		Unspecified type		Total	
No	FR	No	FR	No	FR	No	FR	No	FR
4	38	24	58	24	4.2	1	0	91	34
84	47	50	72	67	12	31	6.5	212	36
66	48	102	65	170	15	262	10	600	25
9	67	14	71	25	24	35	11	83	31
181	45	190	66	286	14	329	10	986	28

for both sexes are given in Table II. The small number of cases of unspecified stroke in the youngest age groups was the result of extensive diagnostic work up in these groups. The very large proportion of subarachnoid and intracerebral haemorrhages is mainly explained by the age of the study population. The increase in incidence with age was very steep for brain infarction and unspecified stroke while it was much less for subarachnoid haemorrhage and intracerebral haemorrhage.

Male/female ratios of incidence rates for stroke by age group are shown in Table III. The sex ratio varied between types of stroke. For subarachnoid haemorrhage there was a female preponderance whereas for intracerebral haemorrhage the ratio varied from a male preponderance in the youngest to an almost equal distribution in the oldest age group. For cerebral infarction and unspecified stroke the male preponderance was pronounced in all age groups. The difference in incidence rates between the sexes was significant for subarachnoid haemorrhage, cerebral infarction and unspecified stroke regardless of age group (Table III). A great difference between the sexes in the age group 15-44 was found also for intracerebral haemorrhage ( $p < 0.01$ ). The male/female ratio of incidence rates showed a male preponderance which increased with age reflecting the increasing proportion of brain infarcts with a high preponderance among older stroke patients.

Incidence rates by age group for each type of stroke are shown in Figs 1-3. Brain infarction and unspecified stroke being considered together. The incidence in brain infarcts and unspecified stroke seemed to manifest itself a decennium later than in men.

Analysis of the case fatality rate shows that most

deaths occurred within 3 weeks of onset of stroke. After 3 weeks and up to one year only 8% died. The overall case fatality rate at 3 weeks was 28% at one year 36% and at 2 years 47% (only stroke patients with onset during 1971 were followed for 2 years) (Table IV). As most deaths occurred within 3 weeks the case fatality rate at 3 weeks was used for all further fatality analyses. The accumulated case fatality rate by sex showed a higher early mortality in women than in men. This was accounted for by a comparatively larger proportion of subarachnoid haemorrhages in female stroke patients. At 2 years this difference disappeared.

Fatality rates (at 3 weeks) by age and type of stroke are given in Table V. No particular differences seemed to exist between the sexes or the age groups but there was a pronounced difference between different types of stroke with a high fatality rate for subarachnoid haemorrhage and particularly for intracerebral haemorrhage and a much lower fatality rate for cerebral infarction and unspecified stroke. The corresponding mortality rates can be calculated from the fatality rates in Table V and the incidence rates in Table II and are shown in Figs 1-3.

Analysis of incidence of stroke and fatality rates by year of registration did not seem to indicate any change with time in incidence rates at large but some decrease in individual types of stroke was noted for both sexes in morbidity from subarachnoid haemorrhage and intracerebral haemorrhage and an increase in cerebral infarction and unspecified stroke. There was no discernible difference between the age groups in these respects. There was a small decrease with time in case fatality for men with subarachnoid haemorrhage and in cerebral infarction and unspecified stroke for both sexes. There was no apparent decrease in the intracerebral haemorrhage fatality rate.

Table VI Annual incidence of stroke by sex per 100 000 inhabitants in selected communities, age group 45-64 years

Community	Years of study	Males		Females	
		45-54 y	55-64 y	45-54 y	55-64 y
Rochester Minn USA (11)	1955-69	158	511	71	261
Espoo Finland (1)	1972-73	206	495	143	250
Fredriksberg Denmark (14)	1971-73	-	450	-	190
Göteborg Sweden (present study)	1970-75	97	316	65	174

## DISCUSSION

Göteborg is well suited for studying the epidemiology of stroke. The city has a well defined population and an accurate census which is updated at two week intervals. Studies of acute cerebrovascular diseases constitute an integral part of the established programmes for the epidemiological studies of other cardiovascular diseases in Göteborg. Until recently only one hospital received emergency cases of somatic illness and by tradition patients with acute illnesses in Swedish cities primarily contact a hospital.

Limiting registration of stroke to subjects up to 65 years of age further increases the likelihood that these patients in fact received hospital care from the onset of symptoms. Furthermore stroke occurs more often as the sole symptom of disease in younger than in elderly persons. Hence the cerebrovascular disease with associated factors can probably be more accurately studied in younger subjects.

On these grounds there were good reasons to believe from the outset of the study that detection of stroke in the population would be effective by the methods used. The validation procedures were performed to show the degree of detection of cases of stroke in the population during the study. These checks showed that no patients with stroke were treated wholly outside hospital that 90-95% of stroke cases treated in hospital were registered and that approximately 95% of all cases of stroke in the population were registered as judged from population screenings. The number of undetected cases in this study would therefore not alter the figures substantially. There was no indication that these constituted any particular group of stroke cases.

The crude incidence rate in this series for the age groups concerned is somewhat higher than in a previous report (10) even when recalculated for the

ages 15-65. The difference may well be due to improved case detection in the present series.

To estimate the total incidence of stroke in a population irrespective of age is difficult. According to a study from 1963 (3) about 1000 stroke patients in Göteborg were under 65 years of age and the total incidence for Göteborg estimated to be approximately 150 per 100 000. However the age composition of the population changes: an increasing proportion being 65 years of age and people below 65 years probably now account for less than one third of cases of stroke. A reasonable estimate of incidence of stroke for Göteborg might be about 200 per 100 000.

Comparison of the total incidence with other studies is not possible but where it fits with the present series the age-specific incidence rates are comparable with those in other series (1, 5, 8, 11, 13, 14, 20) mainly from later years. Our findings suggest a somewhat higher incidence rate in Göteborg than in several other cities for the age groups 45-54 and 55-64. The incidence rates in Göteborg are about 10% higher than the figures reported from Finland for 1971 (1) which were obtained by an interview registration technique. This also applies to comparable figures from Copenhagen for 1971.

It should be noted that the incidence figures for Göteborg include all stroke manifestations including recurrent strokes in some individuals. The figures from Rochester, USA (11) include first strokes only and those from Finland (1) numbers of persons experiencing more strokes during the study period. It is probable that the figures from Göteborg are more reliable estimates. To compare incidence figures from Rochester from 1955-69 is questionable as there may well have continued to be an increase in incidence since then.

Table 6 Annual incidence rate by type of stroke per 100 000 inhabitants in selected communities, age group 55-64 years

	Subarachnoid haemorrhage	Intracerebral haemorrhage	Cerebral infarction + unspecified type	Total
and (1)	49	67	243	358
g. Denmark (14)	16	36	247	299
Sweden (present study)	27	41	173	241

stroke differ greatly between reported series. As a whole there is a male preponderance in stroke cases with age. This was also the case in the present series. This probably reflects the fact that the relative frequency of brain infarcts increases more rapidly with age in men than in women.

The incidence rates reported here are close to those of other investigators (1, 8, 11, 13, 20) both for mortality and for fatality specified by age and sex of stroke. The outstanding differences in the present study are those between the young and old cases and not between the age groups or between the sexes.

The distribution of stroke in this series showed a varying incidence with age and varying sex ratios. There was an evident similarity between cerebral infarction and unspecified stroke for increase in incidence with age as well as for sex ratio and for fatality rate. It is probable that although diagnostically uncertain, the group of unspecified stroke could be considered as a group of cerebral infarction in this connection. Among stroke patients the proportion of subarachnoid haemorrhage and intracerebral haemorrhage was relatively large and the fatality rate was high. For older patients the fatality rate was high owing to a large proportion of these strokes being caused by brain infarcts (+unspecified stroke). It seems evident from these data that in the sex ratio increase in frequency and in fatality rate that subarachnoid haemorrhage and intracerebral haemorrhage and cerebral infarction/unspecified type of stroke constitute distinct disease entities even in epidemiological terms.

The present study, in comparison with other series with respect to type of stroke, is of special interest in the search for clues, but hazardous when diagnostic criteria are used. Age and sex specific incidence rates

for individual types of stroke are comparable, however, when similar criteria of diagnosis of type are used, as in the present study and the studies in Finland (1) and Denmark (14). Incidence rates for each type of stroke for the age group 55-64 years are shown in Table VII. There are not only obvious differences in the total incidence rates but even more so between the individual types of stroke (note that the figures from Goteborg include recurrent strokes). These differences can hardly be ascribed solely to inconsistencies in methodology between the centres. These figures indicate rather that real differences in risk of stroke may exist between these communities. They are consistent with data from the registers of coronary heart disease in Finland and Sweden, showing that in 1971 the incidence of acute myocardial infarction was 2-3 times higher in Helsinki than in Goteborg (9). Mortality rates from vital statistics show that for the age group 55-64 years the mortality from stroke in 1972 was twice as high in Finland as in Denmark and Sweden for both sexes individually and combined. The latter two countries having very similar death rates. So far the prevalence of hypertension and other cardiovascular risk factors in the three communities is known only to a limited degree and comparisons are not possible. Furthermore, it is not known how the risk factors influence the distribution by individual type of stroke in each community. There has been a great deal of interest in prevention (treatment of hypertension, antismoking measures, dietary advice) for the last 10-20 years in Goteborg, but it is not known to what extent these measures have been effective.

The three major types of pathophysiological processes in stroke seem to correspond to three disease entities, each with its own clinical and epidemiological characteristics. Different aetiological factors may operate to varying degrees in each



Furthermore preventive measures need not necessarily influence the total stroke morbidity but may still affect one or more of the types of stroke

Unfortunately studies of sufficiently large numbers of cases with reliable and comparable diagnosis of type of stroke are difficult to achieve. Knowledge of fatality rates and sex ratios together with age specification might to some extent make it possible to discriminate between the important types of stroke so as to allow comparison between different series. But this will be possible only when the detection of cases of stroke in the population is known and close to total so that true incidence figures are obtained. Mortality figures even if age and sex specific cannot reflect the composition of morbidity with regard to type of stroke and are therefore of limited value.

### ACKNOWLEDGEMENTS

This study was supported by grants from the Swedish National Association against Heart and Chest Diseases, the University of Göteborg and the World Health Organization.

### REFERENCES

- Aho K. Incidence profile and early prognosis of stroke. Academic Dissertation Helsinki 1975.
- Bengtsson C. Ischaemic heart disease in women. *Acta Med Scand (Suppl)* 549 1973.
- Broman T & Lindberg Broman A M. Beräkningar rörande det neurologiska rehabiliteringsbehovet i Göteborg. Unpublished 1963.
- Community Control of Stroke and Hypertension. Report of a WHO Meeting. Gothenburg 1971. WHO Internal Document CVD 1 1972.
- Eisenblätter D & Hoppner G. Häufigkeit des Schlaganfalls in der Bevölkerung der DDR. *Dtsch Gesundheitswesen* 32 1064 1977.
- Elmfeldt D, Wilhelmsson L, Tibblin G, Vedin A, J. Wilhelmsson C F & Bengtsson C. Registration of myocardial infarction in the city of Göteborg. *Swedish J Chron Dis* 28 173 1975.
- Elmfeldt D, Wilhelmsson L, J. Wilhelmsson C, Hjalmarson Å & Bergström U. General aspects of secondary prevention of myocardial infarction. *Adv Cardiol* 14 1 1977.
- Frithz G. Studies on cerebrovascular disease. Academic Dissertation Uppsala 1974.
- Furberg C, Romo M, Linko E S, Tibblin G & Wilhelmsson L. Substructure in Scandinavia. A report from Scandinavian heart disease registers. *Acta Med Scand* 1977.
- Harmsen P & Tibblin G. A study of stroke in Göteborg, Sweden. *Acta Med Scand* 1978.
- Matsumoto N, Whisnant J P, Kurland L T, Okazaki N. Natural history of stroke in Minnesota 1955 through 1969. An extension of a previous study 1949 through 1954. *Stroke* 7 211 1976.
- Rinder R, Rouse S, Steen B & Svanberg H. Seventy year old people in Gothenburg. A study in an industrialized Swedish city. Presentation of the study. *Acta Med Scand* 1975.
- Stallones R A, Dyken M L, Farr J, Heyman A, Selzer R & Stamler J. Epidemiology for stroke facilities planning. *Stroke* 7 1 1976.
- Stensgaard Hansen B & Marquardt J. of stroke in Fredrikberg. *Denmark J Med* 1977.
- Tibblin G. High blood pressure management. *Med Scand (Suppl)* 470 1967.
- Vårdcentral i en storslagkraft. *Tyngre och Sjukvård* 1978.
- Vedin A, Wilhelmsson C E, B. L. L. Werko L. Mortality trends in Sweden with special reference to cardiovascular death. *Acta Med Scand (Suppl)* 514 1977.
- Wilhelmsson L, Tibblin G & Werkö L. A preventive study in Gothenburg. *Sweden J Med* 1 153 1972.
- World Health Organization. Cerebrovascular diseases. Prevention, treatment and rehabilitation. Report of a WHO meeting. WHO Tech Rep 1971.
- Zupping R & Roove M. Epidemiology of cardiovascular disease in Tartu. Estonia 1953 through 1973. *Stroke* 7 187 1976.

# Effect of Prolonged In Vivo Administration of Leukocyte Interferon on the Mitogen Responsiveness of Human Lymphocytes

Stefan Einhorn, Henrik Blomgren, Jan Cantell and Hans Strandberg

From Karolinska Hospital, Stockholm, Sweden, and the Department of Virology, Central Public Health Laboratory, Helsinki, Finland

ACT Peripheral lymphocytes from patients receiving interferon (IF) as adjuvant were tested in vitro for response to various mitogens. Prolonged parenteral administration caused no major change of the responses. The ability of IF when added in vitro to lymphocyte response to mitogens was of no major extent by in vivo administration.

Interferon lymphocytes mitogens  
Scand J Clin Lab Invest 1979

More than 100 patients with various diseases have received interferon (IF) at Karolinska Hospital. In late 1971 a clinical trial was started with the object of examining the effect of IF therapy in patients with osteosarcoma

other effects on the immune system (7). It has been shown to suppress lymphocyte response to mitogens and allogeneic cells (8-11). The evidence that IF may interfere with immune functions prompted a study in osteosarcoma patients of 1) whether the administration of IF affects the reactivity of peripheral lymphocytes to mitogens, and 2) if IF therapy modifies the capacity of IF to elicit responses in vitro.

## STUDY POPULATION

Forty patients (15 females, 15 males) with tumors of the long bones without evidence of metastases who received IF as adjuvant therapy ranged from 7 to 30 years (mean 19). A control group was used; it comprised members of the Laboratory staff (9 men, 5 women) aged 26-61 years (mean 34).

## METHODS

### Treatment

Human leukocyte IF (see below) was given for a period of 18 months after primary surgery (amputation, excision, or resection). To 9 of the 40 patients local IF was given (4000-6000 rad) prior to surgery. The IF was administered by intramuscular injection 3 times a week except during the first months and if the patient came to the hospital when it was given or if a day. Each patient received 3 × 10<sup>6</sup> IF units (14). The IF therapy was discontinued in some patients when metastases developed.

### Blood sampling

When the patients were tested before IF therapy, the blood sample was collected after biopsy but before major surgery. From patients receiving radiotherapy blood was drawn when this treatment had been completed. During IF therapy blood was collected 7-10 hours after the last injection.

### Separation of lymphocytes

Lymphocytes were separated from heparinized venous blood by centrifugation on a layer of Ficoll Isopaque (12) and washed twice by centrifugation in Eagle's minimal essential medium (MEM) supplemented with 10% of heat-inactivated human serum (HS) from AB donors. Approximately 90% of the cells were classified as lymphocytes after crystal violet staining; the rest as monocytes and granulocytes.

### Mitogens

The contents of vials containing phytohaemagglutinin (PHA Bacto Phytohaemagglutinin M Difco Lab, Detroit, USA) and pokeweed mitogen (PWM Grand Island Biological Company, NY, USA) were dissolved in 5 ml of MEM. These solutions will be referred to as 100% of PHA and PWM respectively. Concanavalin A (Con A, Sigma Chemical Co., St. Louis, USA) was dissolved in MEM.

**Abbreviations:** IF interferon, MEM Eagle's minimal essential medium, HS human serum, PHA phytohaemagglutinin, PWM pokeweed mitogen, Con A = concanavalin A.

Table I Mitogen response of peripheral lymphocytes to PHA, PWM and Con A before and after IF therapy

Mitogen	Concentration	Incorporated $^{14}\text{C}$ thymidine (cpm)				p
		Patients (n=11)		Controls (n=14)		
		Mean	S D	Mean	S D	
PHA	1.5%	100 600	10 100	71 700	5 600	<0.01
	0.75%	85 200	9 500	57 200	7 900	<0.01
PWM	1.0%	26 600	4 700	30 100	1 400	NS
	0.1%	27 900	5 800	36 900	3 600	NS
Con A	14.0 $\mu\text{g/ml}$	65 200	8 600	74 500	5 400	NS
	3.5 $\mu\text{g/ml}$	13 400	6 500	40 600	4 900	NS

NS=not significant

*Cell culture conditions and thymidine incorporations*

Details of the culture conditions and the measurement of incorporated radioactivity have been published elsewhere (4). Briefly  $2.5 \times 10^5$  lymphocytes were cultured in glass tubes containing 10 ml of MEM supplemented with glutamine 125 units of penicillin 125 µg of streptomycin and 10% of heat inactivated HS. Various concentrations of mitogens were added to some of the cultures others served as controls. IF was added to some tubes at the beginning of the culture period at a final concentration of 1000 units/ml. After 4 days of incubation at 37°C in a humidified 5%  $\text{CO}_2$  air atmosphere 0.4 µCi of  $^{14}\text{C}$  thymidine (specific activity 54 mCi/mM) was added to

each culture. The cultures were completed with trichloroacetic acid and the radioactivity of the material precipitated and expressed in cpm.

Means of duplicate cultures were calculated on an arithmetic basis. Values for cultures without mitogen were subtracted from the values obtained for the corresponding cultures with mitogen added.

*IF preparations*

The methods used for the production of the leukocyte preparations and the measurement of their activities have been described elsewhere (11).

Table II Effect of IF therapy on lymphocyte counts and mitogen responses in vitro presented as the difference between values during and before IF therapy

	Months of IF therapy before 2nd test	Relative lymphocyte count (%)	Relative mitogen response (%)						If rad 2 x 10 <sup>6</sup> /rad
			PHA (%)		PWM (%)		Con A (µg/ml)		
			1.5	0.75	1	0.1	14	3.5	
	3	59	176	241	193	359	140	140	4000
L	3	71	94	62	103	67	93	73	6000
J B	5	74	92	87	83	44	60	33	4000
A R	18	86	71	49	117	56	174	133	4000
U H	10	99	151	79	64	67	116	52	6000
B S	9	82	42	35	101	67	64	32	6000
S L	17	114	94	83	97	86	110	104	6000
O K	12	89	15	50	70	88	107	84	6000
L E	15	87	199	279	100	92	11	86	6000
Median	10	82	94	79	100	67	116	84	
96% confidence limits	3.2	40.0	15.2	15.2	64.1	44.9	60.2	33	
p		NS	NS	NS		<0.05	NS	NS	

\* Months after initiation of IF therapy. FM=free from metastases at the latest control 3-6 years after initiation of therapy. IC=death in intercurrent disease. NS=statistically not significant.

# Effect of withdrawal of IF therapy on lymphocyte count and mitogen response in vitro presented before and after IF therapy

Measurements were made 9-18 months after initiation of IF therapy which lasted for 18 months

Months between withdrawal of IF therapy and last test	Relative lymphocyte count (%)	Relative mitogen response (%)						Irradiation (rads)	Metastases
		PHA (%)		PWM (%)		Con A (μg/ml)			
		1.5	0.75	1	0.1	14	3.5		
3	44	66	59	40	17	47	18	4 000	FM
3	14	111	71	77	51	78	89	4 000	FM
4	184	110	76	151	47	118	78	4 000	
5	39	304	100	118	107	165	575		FM
5	149	122	167	51	77	47	67	6 800	
5	733	783	379	183	779	176	167	4 000	FM
5	103	81	73	104	97	117	174	6 400	FM
6	146	37	39	94	71	14	75		
7	97	234	76	57	95	34	11		
8	124	111	76	98	77	8	78		
36	397	373	393	402	121	147	117		

The changes are statistically significant

after initiation of IF therapy FM free from metastases at the latest control 3-6 years after initiation

medium either concentrated IF or partially purified specific activities of approximately  $2 \times 10^4$  and  $10^5$  units/mg of protein respectively. Preparations IF were used for the in vitro experiments

## Method

Considerable intertest variability of the mitogen response of human lymphocytes even when the lymphocytes obtained from the same donor and are tested under identical conditions. To reduce this variability each patient's lymphocytes was accompanied by a sample of lymphocytes from one of two healthy controls. The mitogen reactivity of the patient's lymphocytes was expressed as a percentage of the value for lymphocytes

## Results

presented in Table I were analysed with a test known as the paired sample *t*-test. The hypothesis was applied to test the hypothesis of a change equal to one against a two-sided alternative

## RESULTS

### Effect of IF therapy on the lymphocyte count and mitogen response

Mitogen responses of the patients' lymphocytes were expressed as relative values (see Methods). Table I gives the absolute  $^3$ H-thymidine incorporation obtained before initiation of IF therapy and after major surgery in 11 osteosarcoma pa-

tients and 14 healthy controls. The response of the patients' lymphocytes to PHA was significantly higher than that of the controls. The two groups were, however, not matched for age and sex. No significant differences could be detected using the other mitogens. The lymphocyte counts before surgery and IF therapy ranged from 1 300 to 3 300 cells/ $\mu$ l of blood (mean  $2 700$ ) (normal range 800-4 000).

In 3 patients lymphocyte counts and relative mitogen responses were examined before, during and after IF therapy (Fig. 1). Two of these patients (A.R. and S.L.) received radiotherapy prior to surgery. All 3 patients received IF during 18 months and were still free from disease 3-5 years after initiation of IF therapy. In these 3 patients the lymphocyte counts remained essentially unchanged. Mitogen responses exhibited large variations but there was no consistent pattern of the changes.

The lymphocyte counts and mitogen responses were determined in 9 patients before and 3-15 months after introduction of IF therapy (Table II). There were no major differences between the mitogen responses recorded on the two occasions with the possible exception of PWM at a concentration of  $0.1 \mu$ g/ml. There was a reduction of lymphocyte counts after initiation of IF therapy but this was not significant. There were no major differences in

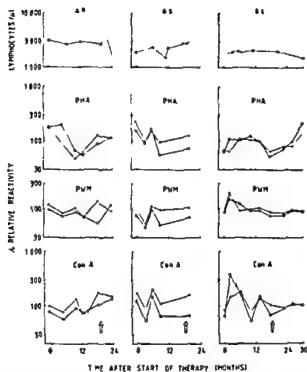


Fig 1 Effect of prolonged administration of IF on the lymphocyte counts and responses to mitogens in 3 patients. Mitogen responses are expressed as a percentage of the corresponding values of a control: PHA 0.75% (O—O) 1.5% (X—X), PWM 0.1% (O—O) 1% (X—X), Con A 3.5 µg/ml (O—O) 14 µg/ml (X—X). Arrow indicates withdrawal of IF therapy.

either lymphocyte counts or mitogen response between the patients who had received radiotherapy and those who had not. Three of the patients developed metastases while receiving *in vivo* administration of IF and one died in intercurrent disease.

The lymphocyte counts and mitogen responses of patients during and after IF therapy (3–7 months after withdrawal) showed no significant differences (Table III). There were no major differences between the patients who had received radiotherapy and those who had not.

#### Effect of IF therapy on the inhibitory activity of IF on mitogen responses *in vitro*

The inhibition of the mitogen response by IF *in vitro* (1000 units/ml) was tested in 2 patients before and after IF therapy. One of them (A.R.) had received radiotherapy prior to IF therapy. No consistent pattern of changes in the ability of IF to inhibit mitogen response *in vitro* were observed in these two patients (Fig. 2).

The ability of IF when added *in vitro* to lymphocytes response to mitogens was tested in 2 patients before and during IF therapy (Fig. 2). Apart from a significant reduction of the response to PHA to inhibit the response of the lymphocytes to PHA, no significant changes due to IF therapy could be observed. There were no major differences between patients who had received radiotherapy and those who had not.

## DISCUSSION

Since IF became available for clinical use a number of trials have been conducted with the aim of examining its effect on various neoplastic diseases (6). It is therefore important to examine whether IF can interfere with normal biological functions.

The results of experiments on laboratory animals and *in vitro* studies on human peripheral lymphocytes have demonstrated that IF can interfere with several functions of lymphocytes. The overall aim of the present investigation was to study the effect of administration of IF on the functional

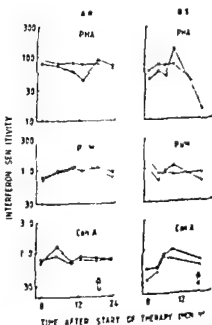


Fig 2 Effect of *in vivo* administration of IF on the inhibitory action of IF *in vitro* on lymphocyte responses to PHA, PWM and Con A in 2 patients. The inhibitory action of IF was determined as the percentage of the stimulation cultures with IF (1000 units/ml) compared to the corresponding values for cultures without IF as in Fig. 1.

Effect of in vivo administration of IF on the ability of human peripheral lymphocytes

expressed as percentage inhibition of stimulation in cultures containing IF (1000 units/ml) compared to control IF. The tests were performed before IF therapy and 3-18 months after initiation of IF therapy. Values are the mean of two experiments. A negative value thus indicates that the lymphocytes have become more sensitive to IF.

Months of IF therapy before and test	Change in ability of IF added in vitro to inhibit lymphocyte response to mitogens						Irradiation (rad)	Metastases
	PHA (%)		PWM (%)		Con A (μg/ml)			
	1.5	0.75	1.0	0.1	14	3.5		
3	+19	+57	65	-47	+17	+15	4 000	
3	+7	8	-75	16	+5	+76		10
6	70	73	-70	-7	-13	17	6 400	
9	15	-86	+57	10	38	50		FM
10	+37	+19	71	71	+3	55	4 000	
17		+10	+37	90	+18	70		FM
15	+51	+35	+7	+4	5	8		FM
18	+13	-11	9	-41	+4	13	4 000	FM
9.5	13	1	-14.5	18.5	3.5	17.5		
13	70.4	86.4	-65.4	90.4	38.7	55.7		
	NS	NS	NS	p<0.05	NS	NS		

Effect of IF therapy. FM, free from metastases at the latest control, 3-6 years after initiation of IF therapy. Death due to recurrent disease. \*  $p < 0.05$  for PHA at 1.5% concentration where a 87.5% confidence limit is shown. † statistically not significant.

peripheral lymphocytes. Since IF in vitro inhibits the response of human peripheral lymphocytes to mitogens (4) the effect of prolonged in vivo administration of IF on the response was studied. In the in vivo administration of IF there were no changes in the lymphocyte counts or their response to mitogens (Tables II and III). Owing to the very large inter- and intrasubject variability in mitogen response, small changes in this response that might have occurred during in vivo administration of IF will probably not have been detected. However, if IF therapy does exert any effects on the mitogen responsiveness of lymphocytes, these effects are relatively small. Of the patients who had received local radiation, which is known to induce lymphopenia (3), there do not seem to be any differences either in lymphocyte counts or in mitogen responses between those who had or had not received radiation (Tables II and III), but the patient numbers are small and this conclusion therefore uncertain.

The effect of IF when added in vitro to inhibit the responses of lymphocytes was not

altered to any major extent by in vivo administration of IF (Fig. 7, Table IV). This finding supports the conclusion that the in vivo administration of IF had no major effect on the mitogen response of the lymphocytes.

It has been shown in the mouse that there is an optimal dose range for the antitumor activity of IF. Too high doses may cause atrophy of lymphoid organs and shorten the survival time (7). If IF has antitumor activity in man, it is therefore important that optimal doses are given. We do not know whether IF administered in higher doses than for the osteosarcoma patients ( $3 \times 10^6$  units of IF daily or 3 times a week) has any suppressive effects on the immune system.

In conclusion, long-term in vivo administration of leukocyte IF in the doses used in this study does not seem to change the mitogen responsiveness of the peripheral lymphocytes to any detectable extent.

## ACKNOWLEDGEMENT

This investigation was supported by a grant from the Cancer Society of Stockholm.

## REFERENCES

- 1 Adamson U, Apansu T, Broström L, Å Cantell h, Einhorn S, Hall k, Ingemarsson S, Nilsson U, Strander H & Söderberg G. Interferon treatment of human osteosarcoma. In: The role of non specific immunity in the prevention and treatment of cancer. Study week of the Pontifical Academy of Sciences, Vatican City. In press 1979.
- 2 Bekesi J G, Roboz J P, Zimmerman E & Holland J F. Treatment of spontaneous leukemia in AKR mice with chemotherapy, immunotherapy or interferon. *Cancer Res* 36: 631 1976.
- 3 Blomgren H, Berg R, Wasserman J & Glas U. Effect of radiotherapy on blood lymphocyte populations in mammary carcinoma. *Int J Radiat Oncol Biol Phys* 1: 177 1976.
- 4 Blomgren H, Strander H & Cantell h. Effect of human leukocyte interferon on the response of lymphocytes to mitogenic stimuli in vitro. *Scand J Immunol* 3: 679 1974.
- 5 Cantell h, Hirvonen S, Mogensen k, E & Pyhälä L. Human leukocyte interferon. Production, purification, stability and animal experiments. In: The production and use of interferon for the treatment and prevention of human virus infections. In vitro Tissue Culture Association, Rockville, Maryland. Monograph no 3: 35 1974.
- 6 Cantell h & Strander H. Human leukocyte interferon for clinical use. In: Blood leukocytes function and use in therapy (ed C F Hogman, P Lindahl, Kressling and H Wigzell) p 73. Symposium Uppsala, Sweden 1977.
- 7 Epstein I. The effects of the interferon system in vitro and in vivo. *Interferon* (ed W E Stewart) p 91. CRR 1977.
- 8 Gresser I, Bandu M E & Bratt R. Interferon and cell division. In: *Interferon: cells, characteristics and origin* (ed J A C) 52-53 1974.
- 9 Hirsch M S, Ellis D A, Prof M S, P H & Chingos M A. Effect of leukemia virus activation in graft vs host culture. *New Biol (London)* 2: 102 1971.
- 10 Hollander M & Wolfe D A. Nonparametric methods, pp 14 and 68. Wiley New York.
- 11 Jondal M, Holm G & Wigzell H. Stimulation of human T and B lymphocytes. I. Large population of lymphocytes forming non-mutagenic sheep red blood cells. *J Exp Med* 134: 273 1972.
- 12 Lindahl Magnusson P, Leary P & Gresser I. Interferon inhibits DNA synthesis in lymphocyte suspensions by physical contact with allogeneic cells. *Nature New Biol* 237: 120 1972.
- 13 Strander H & Cantell h. Production of interferon by human leukocytes in vitro. *Ann Med* 44: 265 1966.
- 14 Strander H, Cantell h, Ingemarsson Jakobsson P, Å Nilsson U & Söderberg G. Interferon treatment of osteosarcoma. *Int J Radiat Oncol Biol Phys* 2: 377 1977.

# Risk Factors for Myocardial Infarction in the Stockholm Prospective Study

A 14 Year Follow-up of the Stockholm Prospective Study  
Triglycerides and Cholesterol

Lars A. Carlson, Lars Erik Bottiger and Per Erik Åhfeldt

From the Gustaf Research Institute and the Department of Internal Medicine  
Karolinska Hospital, Stockholm, Sweden

ACT A 14-year follow up of the Stockholm Prospective Study is reported. A number of 130 new myocardial infarctions (MI) were found in a prospective group of men ( $n = 3189$ ) and another 46 in a retrospective group in the total group ( $n = 3486$ ). Different types of multivariate statistical analyses show that blood pressure, smoking, fasting plasma glucose, cholesterol and triglycerides, ESR, were independent risk factors for MI while body weight index was not. Elevated BP became an important risk factor only after the age of 50. Both age, BP, smoking and the two plasma lipids were entered into the logistic multivariate analysis. Plasma triglycerides were more important risk factor than cholesterol. Quintile analysis showed that the rate of new MIs increased more with increasing triglyceride than increasing cholesterol. In the prospective group, the average rate of MI for men below 60 years was 32 per 1000 person-years and top quintile these rates were 16 and 27 for triglycerides and 27 and 47 for cholesterol. When the men were divided into 4 groups according to both plasma lipids, the rate of new MIs increased successively from group to group. In the retrospective group, both lipids normal only cholesterol high triglycerides high and both plasma lipids

high blood pressure, erythrocyte sedimentation rate, hemoglobin, multivariate analysis, myocardial infarction, plasma cholesterol, plasma triglycerides, prospective, risk factor, smoking.

of the Stockholm Prospective Study (SPS) which started in 1961 was to gain information on the relation between fasting plasma triglyceride and cholesterol values and the future development of atherosclerotic heart disease (IHD). The reason

for this was our findings reported in 1960 that Stockholm survivors of myocardial infarction (MI) not only had a high frequency of elevated plasma cholesterol values but also of raised plasma triglyceride levels (9) which then was a new observation. Two other reports with the same conclusion appeared at that time (3, 4). Our first follow-up SPS after nine years comprised 71 cases of new MIs and indicated that both plasma cholesterol and plasma triglycerides were risk factors for IHD (1).

This second report which is based upon 176 new male infarcts in the total group—whereof 130 in the prospective group—with a follow-up of 14 years corroborates the preliminary findings (11).

## STUDY POPULATION

The initial design of the study and the clinical and laboratory methods have been described in detail (17). The study population is composed of the clientele of a health survey center, an organization which offers the employees a yearly health check-up.

The following examinations and analyses were included. *Case history* with special emphasis on diseases and habits of potential interest in relation to the development of IHD. *Weight* (the height index calculated as weight (kg)/(height (cm)) minus 100). *Systolic and diastolic BP* measured with a mercury manometer at the end of the examination. *ECG* at rest with standard leads and five chest leads (CR<sub>1</sub>-CR<sub>4</sub> and CR<sub>5</sub>). *Chest radiogram* was read by a radiologist. *Haemoglobin* was determined as oxyhaemoglobin. *ESR* was determined according to the original Westergren method. *Urine* was tested for the

Abbreviations: SPS = Stockholm Prospective Study; MI = myocardial infarction; IHD = atherosclerotic heart disease; CVA = cerebrovascular accident; VLDL = very low density lipoprotein; LDL = low density lipoprotein; HDL = high density lipoprotein.



## REFERENCES

- 1 Adamson U, Apan T, Broström L, Å Cantell K, Einhorn S, Hall K, Ingmarsson S, Nilsson U, Strander H & Söderberg G. Interferon treatment of human osteosarcoma. In: The role of non specific immunity in the prevention and treatment of cancer. Study week of the Pontifical Academy of Sciences, Vatican City. In press 1979.
- 2 Bekes J, G. Roboz J, P. Zimmerman E & Holland J. F. Treatment of spontaneous leukemia in AKR mice with chemotherapy, immunotherapy or interferon. *Cancer Res* 36: 631 1976.
- 3 Blomgren H, Berg R, Wasserman J & Glas U. Effect of radiotherapy on blood lymphocyte populations in mammary carcinoma. *Int J Radiat Oncol Biol Phys* 1: 177 1976.
- 4 Blomgren H, Strander H & Cantell K. Effect of human leukocyte interferon on the response of lymphocytes to mitogenic stimuli in vitro. *Scand J Immunol* 3: 679 1974.
- 5 Cantell K, Hironen S, Mogensen K. E. & Pihala L. Human leukocyte interferon: Production, purification and animal experiments. In: The production and use of interferon for the treatment and prevention of human virus infections. *In vitro* Tissue Culture Association, Rockville, Maryland, Monograph no. 3: 35 1974.
- 6 Cantell K & Strander H. Human leukocyte interferon for clinical use. In: Blood leukocytes: function and use in therapy (ed. C. F. Hogman, P. Lindahl, K. Essling and H. W. Gzell) p. 73. Symposium, Uppsala, Sweden 1977.
- 7 Epstein L. The effects of interferon on the immune system in vitro and in vivo. In: *Interferon* (ed. W. E. Stewart) p. 91. CRC Press 1977.
- 8 Gresser I, Banda M. E. & Brown H. Interferon and cell division IX. Interferon and cells. *Characteristics and origin* J Natl Cancer Inst 53: 553 1974.
- 9 Hirsch M. S., Ellis D. A., Proff M. J. P. H. & Chingos M. A. Effect of leukemia virus infection on graft rejection. *Nature New Biol (London)* 240: 10 1973.
- 10 Hollander M. & Wolfe D. A. *Nonparametric methods* pp. 15 and 68. Wiley New York 1973.
- 11 Jondal M., Holm G. & Wigzell H. Studies on human T and B lymphocytes. I. Alteration of lymphocytes forming non-mutual sheep red blood cells. *J Exp Med* 134: 1 1971.
- 12 Lindahl Magnusson P., Leary P. & Gresser I. Interferon inhibits DNA synthesis in lymphocyte suspensions by phagocytosis of allogeneic cells. *Nature New Biol* 273: 10 1977.
- 13 Strander H. & Cantell K. Production of interferon by human leukocytes in vitro. *Ann N Y Acad Sci* 265: 1966.
- 14 Strander H., Cantell K., Jakobson P. Å., Nilsson U. & Söderberg G. Interferon treatment of osseous sarcoma. A pilot trial. *Fogarty International Center Proc* 1977.

Number of men with different categories of MI

MI as a disease is included

	Prospective group (n=3 189)	Pre-existing disease group (n=297)	Total group (n=3 486)
MI	72	17	89
MI + death	34	22	56
MI + death + dead	17	6	23
MI + death + dead + dead	7	1	8
	130	46	176

smoker-1 quit smoking previously heavy  
2 moderate smoker (<20 cigarettes/day)=3  
smoker-5 Age was introduced as years raised to  
power in all regression analyses as this gave  
best fit-value and triglycerides as log concen-  
tration to their skew distribution. The multiple  
regression analysis was carried out with a com-  
puter program which first chooses the independent  
variables with the highest correlation with the dependent  
variable then step by step the variable still outside  
the regression equation which has the highest correlation  
with the variable into the multiple regression equa-  
tion. The calculations were those recommended by  
SAS unless otherwise indicated

## RESULTS

### Causes of death

In the total group 535 men and 163 women died. The causes of death were (no. of men and women) malignant tumours 156/74 MI as a direct cause 104/13 other IHD and heart diseases 11/18 CVA 39/19 gastrointestinal diseases 20/10 vascular disease including thromboembolism 20/10 respiratory disease 21/3 suicides 18/2 accidents 15/5 others 19/13. The causes of death in the total material and their relations to risk factors for MI will be dealt with in a forthcoming study.

Characteristics of subjects in the prospective group later developing MI (mean  $\pm$  S.E.M.)

	All MI			MI alive	MI dead	All healthy 50-59-year old men*
	All ages	<60 y	>60 y			
Number	130	91	39	72	58	
Age (years)	54.4	51.0	63.8*	52.7	56.5***	
	$\pm 0.7$	$\pm 0.6$	$\pm 0.5$	$\pm 0.9$	$\pm 0.9$	
Weight (kg)	96	102	78	98	93	
	$\pm 4$	$\pm 5$	$\pm 7$	$\pm 5$	$\pm 7$	
Height (cm)	171	180	143**	171	170	146
	$\pm 0.07$	$\pm 0.08$	$\pm 0.10$	$\pm 0.09$	$\pm 0.10$	
Weight index (kg/m <sup>2</sup> )	295	297	289	300	287	278
	$\pm 6$	$\pm 7$	$\pm 11$	$\pm 6$	$\pm 10$	
BP (mmHg)	0.98	0.97	1.00	0.99	0.97	0.95
	$\pm 0.01$	$\pm 0.01$	$\pm 0.02$	$\pm 0.01$	$\pm 0.01$	
SBP	149	147	157	148	151	138
	$\pm 2$	$\pm 2$	$\pm 4$	$\pm 3$	$\pm 3$	
DBP	92	92	93	92	91	88
	$\pm 1$	$\pm 1$	$\pm 2$	$\pm 2$	$\pm 2$	
SBP/DBP	91	92	89	91	90	89
	$\pm 0.6$	$\pm 0.6$	$\pm 1.2$	$\pm 0.7$	$\pm 0.9$	
Cholesterol (mmol/l)	8.7	7.3	12**	6.7	11.0**	6.5
	$\pm 0.7$	$\pm 0.6$	$\pm 2.0$	$\pm 0.7$	$\pm 1.3$	

\*p < 0.01 \*\*p < 0.001 Differences were tested between the two age groups and between MI alive and MI dead. Any significant difference indicated.

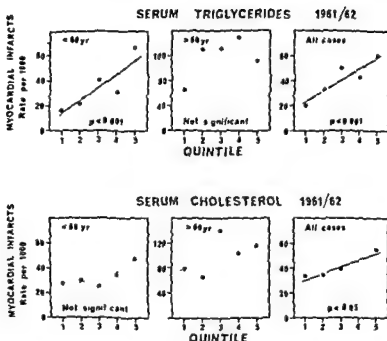


Fig. 1 Rate of MI in different age groups in relation to the distribution of triglyceride and cholesterol in 1961-62. The results of a regression analysis is also given.

#### Categories of MI (Table 1)

In the prospective group 45% died at the first IHD manifestation. The corresponding figure for those with pre-existing disease was 61%.

#### Initial characteristics of IHD subjects

Table II shows some of the initial characteristics of subjects later developing IHD. Mean serum lipid values and BP were higher than in the entire population. There were certain differences between IHD cases below and above 60 years of age which can not be due to differences in age. Particularly striking

from the risk factor point of view are the higher serum triglyceride values for the younger cases.

There were no major differences between the MI dead except that the latter group had a higher FSR.

#### Single risk factor analysis

In the prospective group the rate of MI increased with increasing concentration of plasma triglycerides and cholesterol when the quintile statistics (Fig. 1 and Table III)

Table III Single regression analysis of rate of MI (per 1000) on quintile number for serum variables (prospective group)

	Cholesterol		Triglycerides		Weight/height index		Systolic BP		Diastolic BP		MI		F
	All	<60 y	All	<60 y	All	<60 y	All	<60 y	All	<60 y	All	<60 y	
a <sup>1</sup>	25	20	15	3	32	30	28	21	27	21	22	13	1.7
b <sup>2</sup>	5.2	4.3	8.7	10.6	3.0	0.9	4.3	4.0	4.7	4.0	6.3	6.6	0.1
r <sup>3</sup>	2.1	1.7	3.6	4.3	1.2	0.4	1.7	1.7	1.9	1.6	2.4	2.8	0.1
p <sup>4</sup>	*	ns	*	*	ns	ns	ns	ns	ns	ns	*	*	0.05

<sup>1</sup> Intercept on the y axis.

<sup>2</sup> Linear regression coefficient: rate of infarcts (per 1000) per quintile.

<sup>3</sup> r value for the significance of the regression coefficient.

<sup>4</sup> Statistical significance of the r value: ns = not significant ( $p > 0.05$ ); \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*  $p < 0.001$ .

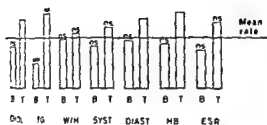


Fig 2 Rate of MI in the prospective group in the bottom (B) and the top (T) quintile for serum cholesterol (Chol) and triglycerides (TG), weight/height index (WHI), systolic (SYST) and diastolic (DIAST) BP, Hb (Hb) and ESR. Statistical significance was tested for the top quintile against the remaining four quintiles combined i.e. B against C-D-E-F against 1-4. The  $\chi^2$  test was used with Yates correction  $p < 0.05$  \* \*  $p < 0.001$

the mean rate as well as its significance was increased for triglycerides with a four fold increase from the bottom to the top quintile in the age group <60 years. Furthermore the quintile analysis showed that the rate of MI rose with increasing values for diastolic BP, Hb and ESR. The weight/height index was however lower for IHD. This analysis is given in Fig 2 which shows a similar picture as above is obtained. It is striking to see that there is not only an increased risk for MI with high triglycerides but also with significantly reduced risk with low triglycerides. The weight/height index on the other hand is a variable in which both the bottom and top quintiles have rates of MI very close to the average rate of 25 per 1000 for the entire prospective group. Analysis of non numerical parameters is given in Table V. Smoking as is well known carries a significantly increased risk for IHD. Neither physical position at work had any significant effect on the rate of development of MI. High education however appeared to protect against IHD.

### Multiple risk factor analysis

The results of multiple logistic regression analysis including the most commonly studied risk factors viz BP, smoking and serum cholesterol and serum triglycerides are given in Table V. The type of analysis age and systolic BP were the most significant risk factors followed by serum triglycerides and serum cholesterol. Cholesterol however appeared as a significant risk factor only in the age group in the total group. As expected the significance of age decreased as the age groups became smaller. Although the number was small in the age group 40-49 years it is striking how the role of BP disappears in this age interval. On the other hand in the age group 50-59 years (not shown in Table V) BP had a very significant influence with  $t$  values around 6. Also the regression coefficients ( $b$  values) for systolic BP rose about 10-fold from the 40-49 to the 50-59 year group being e.g. in the prospective group 0.0020 and 0.0252 respectively. Thus the role of systolic BP as a risk factor for IHD seems to become important only after the age of 50 years.

In the stepwise multiple regression analysis (Table VI) age was the most important single in

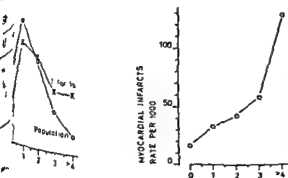


Fig 3 Prospective group. Left Distribution of the total and the MI population by number of risk factors present. Right Rate of MI in relation to number of risk factors present (top quintile for triglycerides, cholesterol, systolic BP, Hb, ESR and smoking).

Table IV Rate of MI (per 1000) in relation to smoking physical activity position at work and education (prospective group all ages)

	Low or no	Higher or yes	Highest
Smoking	20	56*	
Physical activity			
At work	37	47	51
At leisure	48	37	17
Position at work	39	42	41
Education	47	34	17*

All significances were tested against the low (no) group  
\* $p < 0.05$  \*\* $p < 0.001$

dependent risk factor followed by systolic BP smoking plasma triglycerides ESR and Hb while plasma cholesterol did not appear as a significant independent risk factor either in the total or in the prospective group (Table VI)

The multiple logistic regression analysis with all 8 independent variables gave similar results (Table VII) with the same order of magnitude for the  $t$  values of the regression coefficients except that by this statistical method the coefficient for cholesterol was statistically significant

#### Plasma triglycerides and cholesterol as risk factors

To further analyse the role of triglycerides and cholesterol for the development of MI the study population has been divided into 4 groups on the basis of both plasma lipid levels as shown in Table VIII Three different arbitrarily chosen cut-off points for the upper normal limit for each plasma were used in this analysis

Regardless of cut-off points the group with normal lipid levels always had the lowest rate of IHD and the group with elevation of a mixed hyperlipidaemia had the highest rate of IHD. The remaining groups with either high triglycerides or high cholesterol had high triglycerides were intermediate rate of new MI but had in most instances significantly higher values than the normal group. The high triglyceride group had a higher rate of IHD than the high cholesterol group in all of the cut-off points used

#### Multiple risk factors

The effect of the increasing number of risk factors is shown in Fig. 3. Only 18% of the population had no risk factor 35% had one and 25% two risk factors. Only 3% of the population had four or more risk factors. The risk factors rose with the number of risk factors per 1000 in subjects without any risk factor almost 150 in those with 4 or more risk factors a ten fold increase

#### DISCUSSION

The SPS does not comprise a random sample of the Stockholm population and caution must be exercised in generalizing results. To evaluate any bias due to the morbidity of MI in the SPS was common morbidity in the total Stockholm population 1.5 million for which a medical record system exists (1) which is based on death records and the cause-of-death register of the National Bureau of Statistics. The event rate (frequency corrected number of MI) in the SPS

Table V Multiple logistic regression analysis with MI as dependent variable and 8 risk variables ( $t$  values for the regression coefficients and their significances are given)

Age group (y)	n	Age	Systolic BP	Smoking	Triglycerides	Cholesterol
Total group						
20-49	2 512	9.0	7.9	4.9	3.6**	2.9**
50-59	2 243	7.4	7.8	4.6	3.4*	1.9
60-69	1 304	2.7	0.6	2.8	1.3	1.4
Prospective group						
20-49	2 326	7.2	9.9*	4.7	2.0*	1.3
50-59	2 096	5.9*	5.9*	4.4	2.4*	1.1
60-69	1 243	2.4	0.2	2.6	0.8	0.6

\* $p < 0.05$  \*\* $p < 0.01$  \*\*\* $p < 0.001$

Table 1. Stepwise multiple regression analysis with MI as dependent variable (*t* values for the regression coefficients are given only when they were significant)

	Age	Systolic BP	Smoking	Triglycerides	ESR	Hb	Partial <i>r</i> value for cholesterol	Multiple <i>R</i>
Step 1	Rank 1 <i>t</i> 9.6	2 5.1**	3 3.6	5 3.1**	4 3.8*	6 2.5	0.079	0.29
Step 2	Rank 1 <i>t</i> 7.0**	2 4.5***	3 3.6*	4 2.6**	5 3.2	6 2.9	0.027	0.24
Step 3	Rank 1 <i>t</i> 8.0*	2 4.1**	3 4.1***	ns	4 3.2	5 2.8	0.030	0.24
Step 4	Rank 1 <i>t</i> 6.2*	3 3.4***	2 3.8***	5 2.6*	ns	4 2.5	0.024	0.2

\*Step 1 the partial *r* value for triglycerides was 0.035

ns = in which order in sequence the variable was entered into the multiple regression equation (see Methods)

For variable was entered as number six into the regression equation it was not significant ( $p > 0.05$ )

\*  $p < 0.01$      $p < 0.001$

as calculated from this register, was 30.9 per cent. The observed number was 28, a non significant difference ( $P = 0.1$ ). This indicates that the SPS population is not biased in the sense that it had a different morbidity of MI than the general population.

The main reason for undertaking the SPS was to assess the individual role of plasma triglycerides and cholesterol as risk factors for IHD in healthy subjects. We had at the end of the 1950s made the observation that not only plasma cholesterol but also plasma triglycerides were raised in patients (9). This finding has been confirmed in a number of studies (3, 4, 7, 16, 22). Present data confirm our preliminary finding (5, 11) that elevated fasting plasma triglycerides is a significant risk factor for IHD. They substantiate that patients with mixed hyper-

lipidaemia are more prone to develop IHD than those with either high plasma cholesterol alone or high plasma triglycerides alone. The figures in Table VIII also convincingly show that elevation of triglycerides alone is a significant risk factor and more so than elevation of cholesterol alone.

The relatively greater importance of triglycerides than total plasma cholesterol is furthermore evident from the following facts (Table VIII). If the triglyceride cut-off point is raised from 1.8 to 2.0 at a cholesterol of either 280 or 300, the morbidity of MI rises with 30 and 23%. On the other hand if cholesterol is increased from 280 to 300 at a triglyceride level of 1.8 or 2.0 the morbidity will either increase by only 5% or not at all.

There is in general a positive correlation between plasma triglyceride levels and body weight (12, 21). In SPS the *r* value for this correlation, keeping age

Table VII. Multiple logistic regression analysis with MI as dependent variable against 8 independent variables (*t* values for the regression coefficients are given)

	Age	Systolic BP	Smoking	Triglycerides	Cholesterol	ESR	Hb	Weight/height index
Step 1	10.3	8.2	5.8*	3.2**	2.7	4.4	3.7**	0.3
Step 2	8.4*	7.9**	4.8*	3.2	2.6*	3.1**	4.9**	-1.7
Step 3	8.3	6.6*	4.6**	1.8	2.6*	4.4**	3.7	-1.5
Step 4	6.5*	6.0*	4.0*	2.5	2.3	2.3	4.5***	-1.9

\*  $p < 0.01$      $p < 0.001$

Table VIII Rate of events (per 1000) of all categories of MI in relation to plasma cholesterol and triglycerides in men below 60 years of age in the prospective group

% of population with normal lipids	Upper normal values		Lipid groups			
	Cholesterol (mg/100 ml)	Triglycerides (mmol/l)	Both normal	High cholesterol	High triglycerides	Both high
44	260	1.8	17	32	3	4
47	280	2.0	18	32*	4*	5
53	300	1.8	19	35	3*	6
57	300	2.0	20	35	4*	7
66	320	2.0	23	27	43*	10
74	320	2.5	24	34	4*	6

The statistical significance of differences was tested against the group with normal lipid values.

\* $p < 0.05$      $p < 0.01$     \*  $p < 0.001$

constant was 0.23 for men (12). Therefore considering the relation between plasma triglycerides and IHD it is of interest that the weight/height index was totally unrelated to the development of MI.

The number of well documented cases of new MI was sufficiently high in this follow up to permit various kinds of multivariate analysis of the different risk factors. The multiple logistic analysis including 8 independent variables showed that both triglycerides and cholesterol were independent risk factors with similar degree of statistical significance. On the other hand when only five risk factors were introduced triglycerides appeared more strongly as a risk factor than cholesterol. The more complex stepwise multiple regression analysis showed that when all variables were entered into the analysis six were significant independent risk factors for MI. Here plasma triglycerides but not cholesterol appeared as a significant risk factor. From the pure statistical point of view this analysis suggests that the role of cholesterol as a risk factor found in single factor analysis was not due to cholesterol itself but rather to the association between cholesterol and some of the other independent risk factors. In fact cholesterol was significantly correlated to triglycerides, age and ESR with  $r$  values of 0.35, 0.13 and 0.14 respectively. However the fact that cholesterol in this type of analysis did not show up as significant risk factor should not be interpreted to indicate that high plasma cholesterol was not a risk factor as great caution must be exercised in interpretations of multivariate regression analysis particularly when two or more variables are intercorrelated (17).

Furthermore the situation is extremely complex

from the biochemical point of view and the use of multivariate analysis for two variables as plasma triglycerides and cholesterol occur together combined in fixed proportions in plasma lipoprotein particles. Let us first take an increase of 0.5 mmol in plasma triglycerides. This can occur by an increase in the number of very low density lipoproteins (VLDL), the most likely and/or in the number of density lipoproteins (LDL). An increase of 0.5 mmol/l in VLDL triglycerides would mean a VLDL cholesterol and consequently a total cholesterol with 0.25 mmol because of a molar ratio cholesterol/triglycerides of VLDL (10). If on the other hand the increase in triglycerides had been solely due to an increase in the number of LDL particles the corresponding figure would be a much higher increase in plasma cholesterol (10). Thus the obligatory concomitant changes in plasma concentrations of triglycerides and cholesterol and the magnitude and relationship of these changes upon which lipoprotein classification is based. This raises very difficult problems in the interpretation of statistical multivariate analysis of plasma cholesterol and triglycerides. This is further complicated as changes in the third major plasma lipoprotein class, the high density lipoproteins (HDL) will occur as changes in plasma cholesterol and triglycerides.

There is a further complicating factor in the interpretation of statistical results obtained with plasma cholesterol concentrations as the risk factor of HDL cholesterol appear to protect against MI (24) while high levels of LDL and VLDL

have the opposite effect. This renders the interpretation of statistical regression of rate of MI against total plasma cholesterol difficult as a rise in plasma cholesterol may have been due to either an increase in the HDL cholesterol or in the evil LDL cholesterol. As an example of this complexity of the Framingham substudies comprising 815 subjects 49-82 years of age may be cited (18). Not only total plasma cholesterol and HDL cholesterol and plasma triglycerides were measured in that study. Although the Framingham study (20) was the first prospective study to show that total serum cholesterol is a risk factor for IHD in this particular substudy HDL cholesterol was the major risk factor with an independent association with the incidence of IHD while total cholesterol was not associated with the risk (18). Triglycerides were only associated with IHD in females. The role of plasma total cholesterol in spite of its complexity as a risk factor for IHD has been documented in most studies that of triglycerides has been controversial. In a Finnish study of 1648 middle aged men among whom 75 deaths occurred during the seven year follow-up, total serum triglycerides and cholesterol were independent risk factors when analysed by multivariate analysis (26). In the multivariate analysis factors for IHD in the Göteborg study were total cholesterol but not triglycerides emerged as independent risk factor (29). The latter study included however only 44 cases of IHD. In addition to the biochemical reservations discussed above both for the use of multiple regressions with total cholesterol and triglycerides and for the use of plasma cholesterol there may of course be regional differences in risk factors (23) which may explain different results in risk factor studies. In fact when the mean values for plasma cholesterol and triglycerides in SPS (12) and in the Framingham study (29) are compared the triglyceride values were 25% higher in Stockholm while the cholesterol values were very similar. Since plasma triglycerides were determined in both places by the method of Carlson this difference indicates a significant difference in populations between the Swedish cities. Such differences in population profiles may explain different outcomes with regard to the relative importance of one or the other lipid as a risk factor for IHD. The coopera-

tive lipoprotein phenotyping study (13) indeed showed great geographic variability in the relation of total cholesterol and triglycerides to the prevalence of IHD.

It is interesting that both an elevated ESR and a high Hb value appear to be risk factors for MI and that the positive correlations are found even when age is eliminated through the calculation of partial correlation coefficients. An elevated ESR as a coronary risk factor was reported already in 1968 by Natvig et al (25) and Scholtz (27) and again by us in 1972 (11). A slight positive correlation exists between the level of plasma lipids and the ESR values (5) but further studies of patients with asymptomatic hyperlipidaemia (6) showed that the most likely explanation is that the hyperlipidaemia causes silent vascular disease which in turn produces the ESR elevations. The fact that patients who died from their first MI had significantly higher ESR values than those who survived could be explained by more advanced vascular disease in the former. A high Hb value was also found as a risk factor. ESR and Hb values are strongly inversely correlated, i.e. a low Hb contributes to an elevated ESR. Thus there could be no common cause for an elevated ESR and a high Hb value as risk factors for IHD. Nor could the high Hb values and their effect on the IHD be explained as secondary effects of smoking as the positive correlation between MI and Hb values remained even when the effects of smoking had been eliminated by means of multiple regression analysis. It seems more likely that a high Hb value exerts a rheologic effect contributing to vascular damage and thrombosis.

## REFERENCES

- 1 Ahlbom A. Acute myocardial infarction in Stockholm—an area comparison. *Int J Epidemiol* 7: 363 1978.
- 2 Ahlbom A, Rosenqvist U, Böttiger L, E Carlsson L A & Åfelt P E. Occurrence of acute myocardial infarction in Stockholm studied by two different methods. *Acta Med Scand* 205: 271 1979.
- 3 Albrink M J & Man E B. Serum triglycerides in coronary artery disease. *Arch Intern Med* 103: 4 1959.
- 4 Antonis A & Bersohn I. Serum triglyceride levels in South African Europeans and Bantu and in ischaemic heart disease. *Lancet* i: 998 1960.
- 5 Böttiger L E. Erythrocyte sedimentation rate and plasma lipids. *Acta Med Scand* 193: 53 1973.



- 6 Böttiger L E, Carlson L A, Ekelund L G & Olsson A G. Raised erythrocyte sedimentation rate in asymptomatic hyperlipidaemia. *Br Med J* 2: 681 1973.
- 7 Brunner D, Altman S, Loebel K, Schwartz S & Levin S. Serum cholesterol and triglycerides in patients suffering from ischemic heart disease and in healthy subjects. *Atherosclerosis* 28: 197 1977.
- 8 Carlson L A. Determination of serum triglycerides. *J Atheroscler Res* 3: 334 1963.
- 9 — Serum lipids in men with myocardial infarction. *Acta Med Scand* 167: 399 1960.
- 10 — Serum lipoprotein composition in different types of hyperlipoproteinaemia. In: *Advances in experimental medicine and biology* vol 63. Lipids, lipoproteins and drugs (ed. D. Kritchevsky, R. Paoletti & W. L. Holmes) pp 123–129. Plenum Press, New York and London 1975.
- 11 Carlson L A & Böttiger L E. Ischaemic heart disease in relation to fasting values of plasma triglycerides and cholesterol. Stockholm Prospective Study. *Lancet* i: 865 1972.
- 12 Carlson L A & Lindstedt S. The Stockholm Prospective Study I. The initial values for plasma lipids. *Acta Med Scand* (Suppl) 493: 1969.
- 13 Castelli W P, Doyle J T, Gordon T, Hames C J, Hjortland M C, Hulley S B, Kagen A & Zukel W J. HDL cholesterol and other lipids in coronary heart disease. The cooperative lipoprotein phenotyping study. *Circulation* 55: 767 1977.
- 14 Dixon W J (ed.). *BMDP 1R nonlinear regression*. Biomedical Computer Programs, Berkeley 1975.
- 15 Draper N R & Smith H. *Applied regression analysis*. Wiley, New York 1966.
- 16 Goldstein J L, Hazzard W R, Schrott H G, Bierman E L & Motulsky A G. Hyperlipidemia in coronary heart disease. *J Clin Invest* 52: 1533 1973.
- 17 Gordon T. Hazards in the use of the logistic function with special reference to data from prospective cardiovascular studies. *J Chron Dis* 27: 97 1974.
- 18 Gordon T, Castelli W P, Hjortland M C, W B & Dawber T R. The frequency of high density lipoprotein as a protective factor against coronary heart disease. *Am J Med* 44: 717 1973.
- 19 Hald A. *Statistical theory with applications*. Wiley, New York 1969.
- 20 Kannel W B, Castelli W P & McNamara J M. Cigarette smoking and risk of coronary heart disease. Epidemiologic clues to pathogenesis. *Framingham Study J Occup Med* 9: 111 1967.
- 21 Lewis B. *The hyperlipidaemias*. Paoletti R (ed.). Publications, Oxford 1976.
- 22 Lewis B, Chan A, Oakley C M, Fildes I D, P. Anker D M, Oliver A. Serum lipoprotein abnormalities in patients with ischaemic heart disease compared with a control population. *Br Med J* 1: 100 1977.
- 23 Logan R L, Riemersma R A, Tunstall P D, Oliver M F, Olsson A G, Walden C R, S. Kayser L, Callmer E, Carlson L A, L. L. L. Lutz W. Risk factors for coronary heart disease in normal men aged 40. *Framingham Study Lancet* i: 949 1978.
- 24 Miller N E, Thelle D S, Folsom D R, O D. The Tromsø heart study. *Lancet* 1977.
- 25 Naimi H, Borchgrevink C F, Pedersen P A, Schöitz E H & Westlund K. A controlled trial of the effect of broctam on the course of coronary heart disease. *Scand J Clin Lab Invest* 22: 14 1968.
- 26 Pelkonen R, Nikkili E A, Kaulonen S, K. A. Sarna S. Association of obesity with cardiovascular mortality. *Br Med J* 2: 1185 1977.
- 27 Schöitz E H. Sedimentation rate as a factor in coronary risk factor. *Scand J Clin Lab Invest* 22: 14 1968.
- 28 Snedecor G W. *Statistical methods*. Iowa College Press, Ames, Iowa 1970.
- 29 Wilhelmsen L, Wedel H & Torgersson C. Variate analysis of risk factors for coronary heart disease. *Circulation* 48: 940 1973.

# Serum Ferritin during Inflammation A Study on Myocardial Infarction

Gunnar Birgegård Roger Hallgren Per Venge and Leif Widar

From the Departments of Internal Medicine and Clinical Chemistry  
University Hospital Uppsala Sweden

**OBJECT** The ferritin level in serum was investigated in 19 patients with myocardial infarction all with a history of chest pain of less than 4 hours before admission. A significant rise in serum ferritin level was found in 8 patients. The rise was generally small, but that seen in acute infection and not significantly correlated to the size of infarction as estimated by changes in serum levels of myoglobin, ASAT and LDH. The rise started after a mean of 30 hours, but being reached within a week (M 4.3 days). Serum ferritin then fell to 120-300 µg/l (M 190) of the level, where it remained. An initial rise in serum iron levels was unexpectedly seen within 12 hours in 17 patients.

**KEY WORDS** serum ferritin serum iron inflammation myocardial infarction.

Acta Med Scand 206 361-366 1979

Inflammation affects iron kinetics in several ways (1-3). Ishiko et al (14) and Beresford et al (2) have shown that the absorption of dietary iron fell during inflammation and a block in the release of iron from the reticuloendothelial system (RES) cells to the blood has been found both in experimental inflammation and infectious disease (13). Elevated serum ferritin levels in serum during infection and experimental inflammation have been found by several investigators (1, 3, 18, 19, 22, 24, 25). In previous longitudinal studies on patients with acute infections (4) we reported serum ferritin elevations of long duration after the infection had subsided. It was found that serum ferritin starts to rise within the first two days after onset of fever and that the peak level is reached within a week in most patients. It was suggested that the elevation of serum ferritin during inflammation is caused by an enhanced synthesis of ferritin rather than leakage from inflammatory cells. The objectives of the present study were to in-

vestigate if an aseptic inflammation *in vivo* causes an elevation of serum ferritin and how soon after the onset of the inflammatory process this elevation is reached. Myocardial infarction was chosen as a model because it is known to cause an inflammatory reaction and because it is possible to define the starting point of the inflammation rather well, since the dramatic onset of symptoms with central chest pain is easily recognized.

## PATIENTS AND METHODS

**Patients** Nine patients, 7 men and 2 women, 58-83 years old with clinically suspected myocardial infarction were selected for the study. All had been admitted to hospital within four hours of onset of chest pain. After a first examination at the Emergency Department the patients were transported to the Coronary Care Unit of the Department of Internal Medicine. Test samples were collected every third hour during the first 24 hours and then every morning. The observation time varied from 9 to 20 days (M 14). Abnormal myoglobinemia during the first two days was found in all patients (Table I). In five patients (nos 1-5) three other criteria of myocardial infarction were also fulfilled: a history of central chest pain of at least 30 min duration, increase in serum aspartate aminotransferase (ASAT) and development of ECG changes typical of transmural (4 cases) or subendocardial infarction (1 case). S-myoglobin was preferred to creatine kinase (CK) since recent investigations show that S-myoglobin is an indicator of myocardial damage just as early and sensitive as CK isoenzyme MB (28).

Cases 6, 7 and 8 had abnormal myoglobinemia, elevated ASAT values and central chest pain for more than 30 min but unspecific ECG changes. In case 9 the chest pain was left sided and varying, only the first serum sample showed pathological ASAT value and the ECG was unspecific. Two patients had a fatal reinfarction six months (case 1)

**Abbreviations** RES=reticuloendothelial system ASAT=aspartate aminotransferase ALAT=alanine aminotransferase LDH=lactate dehydrogenase CK=creatine kinase

Table I. *Serum clinical and laboratory data in epileptics*

Pat no	Sex	Age (y)	Duration of pain before admission (h)	ECG	ASAT ( $\mu$ kat/l) on day			ALAT ( $\mu$ kat/l) on day			Lactate ( $\mu$ mol/l)
					1	2	3	1	2	3	
1	♂	79	3	Anterior	0.8	7.7	12.9	0.3	1.3	1.4	4.1
2	♂	59	4	Subendocardial RBBB	0.9	1.0	0.5	0.3	0.4	0.4	4.4
3	♂	60	4	Dysrhythmic lateral	0.8	7.7	3.5	0.4	1.6	0.9	3
4	♀	63	3	Dysrhythmic	0.5	4.3	4.4	0.5	0.8	0.8	1.4
5	♂	6	4	Dysrhythmic	0.9	0.9	0.8	0.5	0.5	0.6	1
6	♂	83	3	Unspecific ST-T	1.3	0.9	0.4	0.7	0.5	0.4	4.1
7	♂	60	2	Left septal block	0.4	3.9	1.9	0.1	0.4	0.3	4.4
8	♂	64	3	LBBB	1.5	3.5	1.7	0.5	0.6	0.6	1
9	♀	48	3	Unspecific T	0.9	0.3	0.3	0.3	0.1	0.3	1

and three months later (case 7). Case 5 committed suicide two months later and a healed myocardial infarction was found at necropsy. Case 2 suffered a non fatal reinfarction four weeks later.

Cases 1-6 were given intramuscular injections of various analgesics during the first 74 hours in doses of maximally 7 ml. Further intramuscular injections of analgesics were given to cases 3 and 6 during the second day and to case 1 also during the third day. No other intramuscular injections were given. In case 4 an intracardiac pacemaker system was implanted on day 70. In case 6 cerebral symptoms of lidocaine intoxication were noted 74 hours after admission. Cases 2 and 7 were treated with intramuscular injections of practolol during the first 1-2 days. Serum samples were frozen until assayed. The patients were followed up for 8-70 days.

*Serum ferritin* was measured by the radioimmunoassay method of Wide and Brågård (30) using liver ferritin labelled with  $^{125}$ I by conjugation with an iodinated propionylcadipate according to the principles of Bolton and Hunter (5). Results were expressed in arbitrary units (U) and the mean value for a group of 25 normal men was given the value 100 arb. U/l (range expressed as 95% limits 40-46). The reasons for using arbitrary units were several: there is no international reference standard preparation for ferritin and consequently the normal range varies considerably between laboratories. We had no evidence for the homogeneity of the ferritin preparation used. Incidentally, our normal range corresponds well with that given in  $\mu$ g/l by several well established laboratories (9, 16, 29).

The inter plus intra assay variation calculated as the coefficient of variation from nine repeated assays of control samples at three levels of ferritin concentration was 8% for 19 arb. U/l, 6.5% for 77 arb. U/l and 4.4% for 180 arb. U/l. These three control samples are included in every assay.

*Serum iron* was estimated routinely in the Laboratory of Clinical Chemistry by a Technicon Autoanalyzer. The coefficient of variation was 4% within the normal range.

*Transferrin* was measured by a nephelometric method according to the principles of Lizana and Hellng (20). The coefficient of variation was 3% within the normal range.

*Enzymes* ASAT, ALAT and LDH were determined by the technique recommended by the International Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. The coefficient of variation of the methods were 1.5, 2.0 and 2.0% respectively. The upper limits of the reference ranges were ASAT 0.6, ALAT 0.6, LDH 7.9.

*Serum myoglobin* was measured by a radioimmunoassay (31) using myoglobin labelled with  $^{125}$ I by the technique described by Berman and Hunter (32). The reference value is 47  $\mu$ g/l (range 2-24). The coefficient of variation of the method within the reference range

## RESULTS

When the basal level (mean of the first 24 h ferritin values) was compared with the mean of the 3 highest consecutive values of each patient, the 9 patients showed a significant rise in serum ferritin levels (Student's *t*-test).

Cases 2 and 8 had pathological baseline ferritin levels already on admission and case 4 no rise (Fig. 1). In the others the mean rise from the initial value was 70%. Of the 9 patients normal basal serum ferritin level (46 units) or above normal (patient 4 was a woman, normal limit for women 180 arb. U/l).

It was investigated how soon a significant rise of the basal serum ferritin level occurred. Samples were collected every 24 h during the first 74 hours and a second sample was collected in this time in 3 patients. After the first 74 h test samples were collected every 48 h. In the other 5 patients the mean time between the first and second sample was 30 hours. The mean value was 30 hours from onset of pain

g/l	Hours from admission to peak level of myoglobin
100	9
515	6
1100	0
600	6
870	3
500	12
500	9
1900	0
180	0

1. serum ferritin concentration was reached  
 2. 5 to 8 days (mean 3.8 days)  
 3. 8 patients with a rise in serum ferritin only  
 4. 6 returned to his initial level during the  
 5. remaining at a level 70% higher than the  
 6. level (Table II). In 5 patients a plateau was  
 7. reached 2-8 days (mean 4.8) after the day of the  
 8. rise  
 9. after admission a rise in serum iron of

short duration was noted in 6 of the patients. The peak was reached within 12 hours after admission in all but one (no. 6) who had another peak 24 hours later. This initial peak could in no case be explained by the normal diurnal variation in serum iron. In 5 of the patients the ensuing fall in serum iron to subnormal values within the next few days. Patients 1 and 5 had no fall in serum iron. Patients 1 and 5 had subnormal values on admission.

Transferrin saturation showed slight changes during the study and the values varied between the patients (Fig. 1). No correlation was seen in this small series of patients between the magnitude of serum ferritin peak (either in absolute values or relative to the base level) and the myoglobin, ASAT or LDH peak levels. ASAT and myoglobin peak levels showed good correlation ( $r=0.93$ ,  $p<0.001$ ). There was no correlation between the number of days with fever and the magnitude of the ferritin peak.

## DISCUSSION

Elm et al. (10) have shown that serum ferritin is slightly elevated in man in response to experimental inflammation induced by bacterial endotoxin and

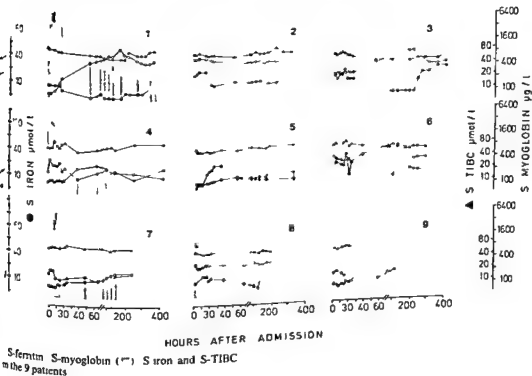


Table II Serum ferritin levels (arb U/l)

Pat no	On admission (basal level)	Peak level	Final level	Difference peak level-basal level		Difference final level-basal level		Hours between onset of pain and first significant ferritin elevation	Serum ferritin at admission
				arb U/l	%	arb U/l	%		
1	80	363	270	483	600	190	238	16	1
2	380	412	350						
3	160	933	300	773	483	140	88	<48	4
4	80	213	122	133	166	42	52	<37	14
5	78	113	89	35	45	11	14	21	23
6	250	539	250	289	115	0	0	<33	34
7	80	174	170	94	118	90	113	24	4
8	270	357	350	87	32	80	30	?	44
9	75	156	95	81	108	20	27	21	?
Mean	161	382	222	247	208	72	70	<30	14

ethocholanolone. The present work shows that this is true also for myocardial infarction. It is notable that the elevations were much smaller than in acute infection (4). Two patients had an abnormally high serum ferritin level already on admission. The reason for this is not known and they have not been investigated afterwards. There was a small but significant rise in serum ferritin level ( $p=0.0005$ ) in one of them and no rise in the other.

The mean interval of 30 hours between onset of pain and the first significant elevation of serum ferritin level given in Table II is probably too long. After the first 24 hours samples were not collected as frequently and there was a time lag of 9–24 hours between the 24 hour sample and the next. The correct time is probably 24–40 hours. This is in accordance with the results of Elm et al. (10) who found that the rise in serum ferritin after experimental inflammation in man started after about 24 hours. Just as in acute infection the peak serum ferritin was reached within a week in most patients (4). Several samples were taken from most of our patients before the ferritin elevation started which made it possible to define a basal level with some certainty in seven. Serum ferritin did not return to its initial level except in one case. At the end of the study it was 14–208% (mean 70) higher than initially. In 5 patients a plateau was reached 2–8 days (mean 4.8) after the peak value. The present study did not last long enough to answer the question whether the ferritin level actually returns to the basal level after some time.

Experimental studies on acute infarction in dogs indicate that the peak levels of serum myoglobin

strongly correlate with the histologic damage (31). In large series of patients the rise in ASAT level correlates to the severity of damage (7, 8, 15) and Hallgren et al. (12) shown a correlation between serum ASAT and myoglobin peak levels in acute infarction. In the present study a correlation was found between serum ASAT and myoglobin peak level but not between these and ferritin peak level ( $r<0.04$ ). Even if our series is very small it does not seem likely that serum ferritin correlates to the size of the myocardial infarction. It is doubtful whether the elevated serum ferritin is caused by a release of ferritin from dead myocardial cells. Instead it could be due to a general enhancement of ferritin synthesis which has been proposed during infection (32). Iron is the natural stimulator of R.E.S. function (32) and during inflammation iron is released within the R.E.S. by several mechanisms. It has been shown that iron is released from the R.E.S. block in the release of iron from the R.E.S. (33). It has been shown to exist during inflammation and inflammation causes an accumulation of injected  $^{59}\text{Fe}$  in the ferritin of the spleen in the rat (21). The question whether elevated serum ferritin levels are due to a release of ferritin from dead myocardial cells or are the result of an enhanced synthesis may be elucidated by a study of the immunoreactivity of the serum ferritin. A radioimmunoassay for ferritin and a radioimmunoassay for ferritin which was however not available.

A fall in serum ferritin was seen within 2–5 days in 4 of our 9 patients. A fall in serum ferritin

gly enough there was an initial rise in iron within the first 12 hours in 7 patients and coincides in time with the myoglobin rise since myoglobin is an iron containing protein. This could be suspected to cause the rise in iron. There is no correlation, however, between the magnitude of the myoglobin and serum iron. Furthermore, myoglobin can carry only 4 atoms per molecule and even if up to 5000 myoglobin is released in some patients this cannot explain a rise in serum iron of up to 18  $\mu$ g/l. The ensuing fall in serum iron in most cases occurs at the same time as the elevation in iron. Iron starts. The suggested transport of iron from plasma into RES by lactoferrin proposed by Linder et al. (26) could therefore theoretically explain the importance for an accumulation of iron with myoglobin and an eventual stimulation of ferritin synthesis.

## ACKNOWLEDGMENT

This study was supported by grants from the Swedish Medical Research Council.

## REFERENCES

1. Cook J D & Williams P. Serum ferritin concentration as an index of iron stores in rheumatoid arthritis. *J Clin Pathol* 27: 786, 1974.
2. Neale R J & Brooks O G. Iron metabolism and pyrexia. *Lancet* i: 568, 1971.
3. Cook J D & Bieher M. Detection of ferritin as a circulating tumour associated antigen in Hodgkin's disease. *Natl Cancer Inst Monogr* 36: 147, 1973.
4. Hallgren R, Killander A, Strom M, Venge P & Wide L. Serum ferritin in infectious diseases. *Scand J Haematol* 21: 333, 1978.
5. Linder M A & Hunter W M. The labelling of proteins with high specific radioactivities by conjugation to a protein containing alkylating agent. *Biochem J* 133: 529, 1974.
6. Wright G E & Lee G R. The anaemia of chronic disorders. *Br J Haematol* 21: 147, 1971.
7. Masson P L. Correlation of mortality rate and serum enzymes in myocardial infarction. *Br Heart J* 6: 643, 1971.
8. Relation of cardiac complications to SGOT level in myocardial infarction. *Br Heart J* 34: 890, 1972.
9. Cook J D, Lipschitz D A, Laughton Ch Miles M & Finch C A. Serum ferritin as a measure of iron stores in normal subjects. *Am J Clin Nutr* 27: 681, 1974.
10. R J Wolff S M & Finch C A. Effect of induced fever on serum iron and ferritin concentrations in man. *Blood* 49: 147, 1977.

11. Fillet G, Cook J D & Finch C A. Storage iron kinetics. VII. A biological model for reticuloendothelial iron transport. *J Clin Invest* 53: 1527, 1974.
12. Hallgren R, Cullhed I, Roxin L E & Venge P. Myoglobinemia after myocardial infarction: influence of renal function. *Eur Cardiology* in press, 1979.
13. Hellmeyer L, Keldrich W & Wöhler F. Der Eisenstoffwechsel beim Infekt und die Entgiftungsfunktion des Spleens. *Dtsch Med Wochenschr* 45: 1965, 1958.
14. Hershko C, Cook J D & Finch C A. Storage iron kinetics. VI. The effect of inflammation on iron exchange in the rat. *Br J Haematol* 28: 67, 1974.
15. Kibe O & Nilsson V J. Observations on the diagnostic and prognostic value of some enzyme tests in myocardial infarction. *Acta Med Scand* 182: 597, 1967.
16. Leyland M J, Ganguly P C, Blower D & Delamore I N. Immunoradiometric assay for ferritin in human serum. *Scand J Haematol* 14: 185, 1975.
17. Linder M C, Horowitz M, Ruettinger R T & Munro H N. Iron induction of electrophoretically different ferritins in rat liver, heart and kidney. *Biochim Biophys Acta* 200: 442, 1970.
18. Lipschitz D A, Cook J D & Finch C A. A clinical evaluation of serum ferritin as an index of iron stores. *N Engl J Med* 290: 1213, 1974.
19. —. Ferritin in formed blood elements. *Proc Soc Exp Biol Med* 148: 358, 1975.
20. Lizana J & Hellsing K. Polymer enhancement of automated immunological nephelometric analysis as illustrated by determination of urinary albumin. *Clin Chem* 20: 415, 1974.
21. Mazur A, Carleton A & Carlsson A. Relation of oxidative metabolism to the incorporation of plasma iron into ferritin in vivo. *J Biol Chem* 236: 1109, 1961.
22. Reitsman K R & Dietrich M R. On the presence of ferritin in the peripheral blood of patients with hepatocellular disease. *J Clin Invest* 35: 588, 1956.
23. Roxin L E, Venge P, Fridman G & Hallgren R. Radioimmunoassay of human myoglobin in serum and urine. *Scand J Clin Lab Invest* in press, 1979.
24. Simoes M A, Addiego J E & Dallman P R. Ferritin in serum: diagnosis of iron deficiency and iron overload in infants and children. *Blood* 43: 581, 1974.
25. Simoes M A & Dallman P R. New kinetic role for serum ferritin. *Br J Haematol* 28: 7, 1974.
26. van Snick J L, Markowitz B & Masson P L. The ingestion and digestion of human lactoferrin by mouse peritoneal macrophages and the transfer of its iron into ferritin. *J Exp Med* 146: 817, 1977.
27. van Snick J L, Masson P L & Heremans J F. The affinity of lactoferrin for the RES as the molecular basis for the hypsideremia of inflammation. In: *Proteins of iron storage and transport in biochemistry and medicine* (ed R R Christen) p. 433. North Holland Publishing Co., Amsterdam, 1975.
28. Sylvén C & Bendz R. Myoglobin creatine kinase and its isoenzyme MB in serum after acute myocardial infarction. *Eur J Cardiol* 8/4: 5, 515, 1978.

- 29 Unger A & Hershko C Hepatocellular uptake of ferritin in the rat *Br J Haematol* 28: 169 1974
- 30 Wade L & Birgegård G A solid phase radioimmunoassay method for ferritin in serum using  $^{125}\text{I}$  labelled ferritin *Ups J Med Sci* 82: 15 1977
- 31 Willerson J T, Poliner L, Buja L M, Waterman L M, Gomez Sanchez C E, Tempelton G H & Stone M J Myoglobinemia due to acute myocardial infarction *Am J Med* 24: 422 A 1976
- 32 Zahring J, Baliga B S & Yoon S A mechanism for translational control of ferritin synthesis by iron *Proc Natl Acad Sci USA* 73: 897 1976

# Clinical Features in Patients with Recurrent Myocardial Infarction

Rurik Lofmark

From the Department of Medicine, Karolinska Institute at Huddinge Hospital,  
Huddinge, Sweden

A retrospective investigation of 420 who had survived the acute phase of an infarct on revealed 63 reinfarctions (in 57 within three months. Twenty-eight patients out reinfarct on during the same period survived three months without reinfarction. Infarction patients were significantly more often had more frequently a history of previous infarct on and hypertension, and their infarctions were more often non-transmural and localized to the anterior wall of the heart. Of each patient that was registered nearest the reinfarct on during hospitalization or discharge showed more often negative T

wave or R wave progression and/or a localized T wave inversion followed by a T wave inversion and/or raised S-GOT values with a maximum about 4 h after onset of symptoms. Findings at autopsy of a reinfarct on at the stage corresponding to the onset of symptoms. S-GOT was determined twice daily during the first three days. A 12-lead ECG (leads I, II, III, aVF, V1, V2, V3, V4, V5, V6, CR, CR, CR, CR, CR, CR, CR, CR) was performed every morning for three days and then twice a week.

The infarct was considered to be anterior if the following changes were present in leads CR<sub>1</sub>, lateral if in leads aVL and/or CR<sub>2</sub> and inferior if in leads II, III, and/or CR<sub>3</sub>. Transmural infarct on was considered when pathologic Q-wave or R wave progression appeared.

The ECG of each patient that was registered prior to reinfarct on during the stay in hospital or prior to discharge was examined for Q wave changes, R wave changes, ST elevation, T wave inversion, amplitude of the T wave, and combinations of Q-, R-, ST- and T wave changes.

T waves cannot be evaluated properly in the presence of bundle branch block (BBB), preexcitation (WPW), left ventricular hypertrophy (LVH) or atrial fibrillation/flutter because these conditions affect the T waves appearance.

The ECGs of the reinfarct on patients were compared with those of the patients who survived three months without reinfarction. The ECGs in the comparison were registered at the same number of days after the infarct on.

The study period extended over three months following AMI. Almost all survivors were followed at the Outpatient Department. Reinfarct on was diagnosed by the same criteria as above.

The significance of differences between mean values was tested by Student's *t* test. The  $\chi^2$  test (with Yates correction) was used to test differences between relative numbers.

## RESULTS

### Reinfarction

Of the 420 AMI patients discharged alive from the CCU, 78 died within three months without proven

## PATIENTS AND METHODS

Patients with AMI initially treated in the Coronary Care Unit (CCU) at Huddinge Hospital 1972-76 (420) were followed up from the CCU. The diagnosis of AMI was based on: 1) prolonged chest pain, frank pulmonary edema, syncope, and 2) appearance of an abnormal Q

Abbreviations: AMI, acute myocardial infarction; CCU, coronary care unit; BBB, bundle branch block; WPW, preexcitation; LVH, left ventricular hypertrophy.



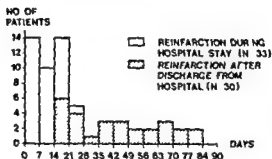


Fig 1 Interval between infarction and reinfarction

reinfarction (heart failure 14 sudden death <24 hours after onset of symptoms 8 cardiac rupture 2 other reasons 4). Autopsy was performed in 15 patients (57%). Another eight had been examined before death without suspicion of reinfarction. In three patients neither a clinical nor a post mortem examination was performed.

Fifty-seven patients (12%) reinfarcted within three months: four of them twice and one thrice. Thus a total of 63 reinfarctions occurred (reinfarction group); the majority (68%) within four weeks and about half of them (48%) after discharge from hospital (Fig 1). Of the 57 reinfarction patients 16 (28%) died during the hospital stay and 15 (88%) were autopsied. A total of 335 patients survived three months without reinfarction (survivors).

There was a significant predominance of women, patients with previous myocardial infarction, hypertension, anterior and non-transmural infarction among those who later reinfarcted (Table 1).

Postinfarction angina pectoris was registered in most of the patients during the hospital stay and the reinfarction group showed a tendency towards a higher frequency of angina (68%  $n=50$ ) than the survivors without reinfarction (53%  $n=312$ ).

The maxima of S-GOT for the primary infarctions and reinfarctions could be compared in 50 cases and no difference was found ( $157 \pm 84$  and  $135 \pm 74$  U/l respectively  $p > 0.1$ ).

In 46 cases both the primary infarction and the reinfarction could be localized to a specific wall of the left ventricle (anterior, lateral or inferior). One and the same wall was affected in both instances in 33 cases but not in 13 ( $p > 0.05$ ).

## ECG

The ECGs registered prior to reinfarction during the stay in hospital or prior to discharge and the

Table 1 Characteristics of reinfarction and survivors with reinfarction

	Reinfarction group (N=63)	Survivors without reinfarction (N=335)
Age (y)*	58	58
Women (%)	52	48
Previous AMI (%)	33	10
Previous angina pectoris (%)	68	53
Diabetes mellitus (%)	9	10
Hypertension (%)	28	25
Medication on admission		
Digitalis (%)	33	10
Quinidine (%)	3	3
$\beta$ -blockers (%)	19	10
Diuretics (%)	41	30
Anterior AMI (%)	23	10
Inferior AMI (%)	19	10
Transmural AMI (%)	48	10
S-GOT max (U/l)*	157	135
ECG		
Showing atrial fibrillation/flutter BBB WPW or LVH (%)	33	10
QRS frequency/min*	75	75
Medication after AMI		
Digitalis (%)	33	10
Quinidine (%)	11	3
$\beta$ -blockers (%)	19	10
Diuretics (%)	41	30

\* Mean  $\pm$  SD

\* $p < 0.01$  \*\* $p < 0.001$

time matched control ECGs were compared. No significant changes, such as presence or absence of Q waves or ST segment elevation, were found to differentiate the reinfarction group from the control group.

However, when the study of the T wave was interfered with by BBB, LVH, WPW or atrial fibrillation/flutter, a negative T wave was more common in the reinfarction group (43/49 (88%) against 192/312 (61%) in the control group. Thirty-nine (80%) and 161 (51%) had a QRS complex with a negative T wave in the lead with negative T wave in the

## DISCUSSION

Reinfarction is the most common cause of death among patients who die after having survived the acute phase of a myocardial infarction. The autopsy rate (92%) is a fresh finding. It was found in two thirds of the patients who died two years after a myocardial infarction.

identifiable cause of death was found at )

dictability of reinfarction would thus be interest for the prevention of recurrence or a closer study of the course of pre a Many clinical factors known to pre lity after a myocardial infarction (1 3 5 ) have either not been tested or have to be ineffective as predictors of rein 8)

dy was confined to three months postin ainly because this period is important for on rehabilitation and a return to a normal reinfarctions also occur within these first 8) and the mortality from reinfarction de th time being about 50% in the first three d about 20% thereafter (9)

her series a reinfarction was more com ents with previous AMI or hypertension which probably explains why medication eptor blockers and diuretics was more n the reinfarction group The majority of it reinfarction patients sustained a non l primary AMI Such AMIs have previ l considered to have a better prognosis it has been observed that survivors of nural infarction have a higher long term igma pectoris recurrent infarction and ath than survivors of transmural infarc 70)

: women in the present series more often l is not clear but a similar tendency has been presented (17) The primary infarc ore often localized anteriorly in the pa reinfarcted than in the controls The : this is not obvious and similar findings een published

et al (16) have attempted to predict rein / means of the ECG They observed that ine patients with recurrent postinfarction l simultaneous transient ST segment ele penenced a recurrent AMI within six seventh patient reinfarcted within five

facebo group of the Coronary Drug Pro i correlation was found between negative m the ECG and mortality and sudden e months to three years following the ot with reinfarction despite the fact that e mortality was attributed to coronary ase

Postinfarction angina was not systematically reg istered in this retrospective series so no conclu sions can be drawn

# REFERENCES

- 1 Chapman B L & Grav C H Prognostic index for myocardial infarction treated in a coronary care unit *Br Heart J* 35 135 1973
- 2 Coronary Drug Project The prognostic importance of the electrocardiogram after myocardial infarction *Ann Intern Med* 77 677 1972
- 3 Elmfeldt D Wilhelmsen L Wedel H Vedin A Wilhelmsen C & Tibblin G Primary risk factors in patients with myocardial infarction *Am Heart J* 91 412 1976
- 4 Helmers C Short and long term prognostic indices in acute myocardial infarction *Acta Med Scand (Suppl)* 555 1974
- 5 Helmers C Hofvendahl S Lundman T Rehnqvist N Sjogren A & Wester P O Prediction of sudden death in patients discharged after acute myocardial infarction *Eur J Cardiol* 3 187 1975
- 6 Hofvendahl S Influence of treatment in a coronary care unit on prognosis in acute myocardial infarction *Acta Med Scand (Suppl)* 519 1971
- 7 Kjoller E Long term prognosis after acute myocardial infarction *Dan Med Bull* 23 238 1976
- 8 Levy W K Cannon C S & Cohen L S Prognosis of subendocardial myocardial infarction *Circulation (Suppl)* 2 107 1975
- 9 Lie K J Tans A C Loundtz W J Durrer D & Wellens H J J Immediate prognosis in recurrent myocardial infarction *Lancet* i 647 1975
- 10 Lundman T & Helmers C Prognostic factors in the Swedish collaborative CCU study In *Acute and long term medical management of myocardial ischaemia* (ed Å Hjalmarsson and L Wilhelmsen) pp 114-119 Liudgren & Soner Molndal 1978
- 11 Madias J E & Gorlin R The myth of acute mild myocardial infarction *Ann Intern Med* 86 347 1977
- 12 Moss A J DeCamilla J Engstrom F Hoffman W Odoroff C & Davis H The posthospital phase of myocardial infarction *Circulation* 49 460 1974
- 13 Norris R M Brandt P W T Caughey D E Lee A J & Scott P J A new coronary prognostic index *Lancet* i 274 1969
- 14 Norris R M Caughey D E Mercer C J & Scott P J Prognosis after myocardial infarction *Br Heart J* 36 786 1974
- 15 Peel A A F Semple T Wang I Lancaster W M & Dall J L G A coronary prognostic index for grading the severity of infarction *Br Heart J* 24 745 1962
- 16 Stenson R E Hamm M D Zaret B L & McGowan R L Transient ST segment elevation with postmyocardial infarction angina prognostic significance *Am Heart J* 89 449 1975
- 17 Vedin A Hjartinfarkt i Goteborg 1968-1970 *Elan ders Kungsbäcka* 1974
- 18 Vedin A Wilhelmsen L Wedel H Pettersson

- B Wilhelmsson C Elmfeldt D & Tibblin G Prediction of cardiovascular deaths and non fatal reinfarctions after myocardial infarction *Acta Med Scand* 201 309 1977
- 19 Vedin A Wilhelmsson C Elmfeldt D Saveri Soderbergh J Tibblin G & Wilhelmsson L Deaths and non fatal reinfarctions during two years follow up after myocardial infarction *Acta Med Scand* 353 1978
- 20 Venkatachalaratnam D & Lofmark R Clinical features early and late after acute subendocardial myocardial infarction and transmural myocardial infarction *Acta Med Scand* 4 226 1973

# Effect of Plasma Free Fatty Acid Lowering on Exercise Tolerance and ST Segment Depression in Patients with Angina Pectoris

E Loogna L Kaijser and L A Carlson

Departments of Clinical Physiology and Internal Medicine and King Gustaf V Research Institute Karolinska sjukhuset Stockholm Sweden

The effect of a single oral dose of a lowering drug (5-(3-pyridyl) tetrazole) not act by conversion into nicotinic acid tolerance and ECG reaction was studied blind basis in 15 men with stable angina exercise was performed on a bicycle er the sitting position with a load increase m In addition to ECG, time to onset of and to termination of exercise because of if pain was recorded 5 (3 pyridyl) tet raised plasma FFA during exercise from pool/I It reduced significantly the ST at corresponding work loads and permit tents to exercise 0.6 min longer, corre 17% higher work load, before the onset un However absolute exercise time was cantly increased The most probable ex of the improved performance is a de and increased carbohydrate oxidation emic heart, although a contribution may e from hemodynamic effects of the drug, e effects on myocardial metabolism but involving heart rate and BP The lack of a t effect on performance time may have to general fatigue

plasma FFA angina pectoris exercise toler depression metabolic intervention Scand 206 371 1979

to which different substrates are taken blized by the heart muscle is dependent on d concentration of the substrate in ques also on the blood concentration of alterna strates (19) Thus any change in plasma y acid (FFA) concentration would alter the and utilization of FFA but also in the d reaction the uptake of glucose (10 11 14 most situations plasma FFA is the pre

dominant substrate of myocardial oxidative me tabolism However for a given energy yield the combustion of lipids requires more oxygen than the combustion of carbohydrates as shown in animal experiments (13) and suggested by studies in man (18)

A procedure which increases the relative utiliza tion of carbohydrates by the heart muscle would therefore offer a possibility to improve myocardial performance in patients with ischemic heart dis ease This might be achieved by drugs such as nicotinic acid which inhibit lipolysis in adipose tis sue thereby lowering the plasma FFA concentra tion (1) Thus  $\beta$  pyridyl carbinol (Ronicol<sup>®</sup>) was found to reduce the extent of ischemic ECG changes in experimental coronary occlusion (9) In patients with angina pectoris nicotinic acid was shown to permit a higher angina threshold during atrial pacing (6) Luxton et al (12) on the other hand found a reduced ST segment depression dur ing exercise but no effect on exercise tolerance by a nicotinic acid analog (5 fluoro 3 hydro-methylpy redimhydrochloride) in patients with stable angina pectoris The absence of effect on exercise toler ance is surprising if the effect on ST depression is to be taken as evidence of reduced oxygen deficit However nicotinic acid and its analogs have hemodynamic in addition to antilipolytic effects (11 17) which might obscure the implications of the results

The aim of the present study was to investigate the effect of 5 (3 pyridyl) tetrazole (P 5722) on exercise tolerance and exercise ST depression in patients with angina pectoris P 5722 is an antili polytic drug with minimal hemodynamic effect (7) Our aim was to find out if any reduction of ST depression was paralleled by increased exercise

Heart rate beats/min

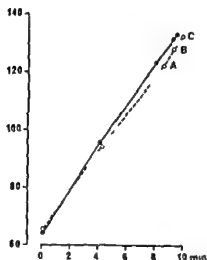


Fig. 1 Heart rate at rest after 4 min exercise at the occurrence of chest pains (A) at the highest common load with and without P 5722 (B) and at termination of exercise because of chest pains (C) without and with P 5722

tolerance P 5722 unlike e.g. Ronicol<sup>®</sup>, exerts its effect without previous conversion to nicotinic acid. In fact it is almost unchanged in the body and about 80% of the dose administered per os can be recovered in the urine.

### PATIENTS

men aged 33–66 years (mean 51) with stable pectoris since at least 3 months were studied. Seven of them had had a myocardial infarction more than year before the investigation. All patients had horizontal or downward sloping ST depression of at least 1.5 mm in a left precordial lead during an exercise tolerance test (5). No patient had signs of heart incompetence, neither did any of them have hypertension, defined as systolic pressure above 160 and diastolic above 100 mmHg. Four patients had been on  $\beta$  blocker and six patients on antilipolytic drug treatment. However, all drugs were withdrawn one month before the study.

### PROCEDURES

One month before the study the patients underwent an exercise tolerance test in the sitting position on a bicycle ergometer in which the load was increased by 10 W/min during continuous ECG recording. The time at which chest pain occurred was noted and the test was discontinued when intolerable chest pains had developed. Each patient then performed two exercise tests on two consecutive days after administration on a double blind basis of P 5722 or placebo. On both occasions the patient reported to the laboratory at 8.00 a.m. after an overnight fast. A short

catheter was introduced in a subcutaneous vein and sampled for FFA determination at 0, 2, 4, 6, 8 and 10 min. P 5722 or placebo were given per os. The load on the bicycle ergometer was increased by 10 W/min every 2 min selected so that intolerable chest pains would develop after about 8 min as judged from the previous test. Heart rate was recorded before (CR<sub>1</sub>), at 2 min (CR<sub>2</sub>), at 4 min (CR<sub>3</sub>) and at 6 min (CR<sub>4</sub>) (chest head leads from the same chest grid for 10 min after exercise). Systolic and diastolic BP during exercise were recorded by the cuff method. Venous blood for FFA analysis was taken at the end of exercise. Plasma FFA was estimated by the <sup>3</sup>H method (4). The ST level (lead CH<sub>2</sub>) was taken to represent the ST level of the chest leads. P 5722 was provided by Dr C. Sjöström, Central Research, Sandwich, Kent, UK.

Unless otherwise stated, values for the 12 placebo groups are given as mean  $\pm$  SE. The use of differences between the groups is based on paired *t* test.

### RESULTS

**Plasma FFA.** Basal plasma FFA was 422  $\pm$  49  $\mu$ mol/l in the placebo group. At the end of exercise it was 490  $\pm$  61  $\mu$ mol/l in the placebo group, which was not significantly different from basal ( $p > 0.05$ ), while with P 5722 it was 299  $\pm$  38  $\mu$ mol/l ( $p < 0.01$ ).

**Exercise tolerance.** With placebo the exercise tolerance was 7.9  $\pm$  0.9 min corresponding to 790  $\pm$  110 W and with P 5722 after 8.5  $\pm$  1.0 min corresponding to 120  $\pm$  11 W. The difference was significant ( $0.05 < p < 0.1$ ). Exercise was terminated

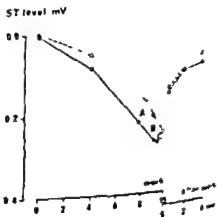


Fig. 2 ST level in CH<sub>2</sub> at rest and during exercise at the occurrence of chest pains (A) at the highest common load with and without P 5722 (B) at the termination of exercise because of chest pains (C) without and with P 5722 after work with placebo and with P 5722

mins after 9.4 ± 0.9 min with placebo and 0.9 min with P 5722 corresponding to 1.7 ± 1.0 W respectively. The difference is significant ( $p > 0.05$ ) (Fig. 1). Heart rate at rest was  $64 \pm 6$  with placebo and  $67 \pm 5$  with P 5722. In relation to work load, heart rate in both groups was less with P 5722 than with placebo. At the highest common work load it was  $177 \pm 8$  and  $131 \pm 6$  with placebo ( $p < 0.05$ ). At the onset of chest pains and on termination of exercise did not differ significantly between P 5722 and placebo. At rest the systolic blood pressure was  $139/84$  mmHg with P 5722 and  $137/85$  mmHg with placebo. On termination of exercise the systolic blood pressure was  $140 \pm 4$  and  $142 \pm 4$  mmHg respectively. However immediately after exercise the systolic blood pressure was higher with than without P 5722,  $146 \pm 6$  and  $138 \pm 5$  mmHg respectively, while the diastolic pressure did not differ (Fig. 2). At rest the ST level was zero with placebo and placebo. In relation to work load the ST level was depressed significantly less with P 5722 than with placebo and at the highest common work load was  $2.1$  mm and  $2.7$  mm respectively. At the onset of chest pains the level was  $2.1$  mm with P 5722 and  $2.2$  mm with placebo and on termination of exercise it did not differ between the two groups,  $2.55$  mm and  $2.5$  mm respectively ( $p > 0.05$ ). Over the first 10 min of exercise the level did not differ significantly between P 5722 and placebo. Occasional premature beats were recorded during exercise in some patients with no difference between P 5722 and placebo.

## DISCUSSION

Produced a decrease in plasma FFA concentration during exercise to slightly more than half that found at rest, which was similar in magnitude although of slightly shorter duration than that found with 100 mg nicotinic acid per os (7). Most patients had a slight skin flush which means that the action of the drug was not double blind in this sense. However the flush and the vascular effects are far less pronounced than those produced by nicotinic acid (7). Plasma FFA lowering would

permanently increase myocardial performance in patients with angina pectoris since it decreases the uptake and oxidation of fatty acids thereby increasing the utilization of carbohydrates (10). The oxidation of carbohydrates yields more energy per unit of oxygen than lipids. In accordance with this it has been shown that the heart rate which can be achieved by atrial pacing before chest pains occur is increased by nicotinic acid (6). However the extent to which improved metabolism is of practical importance for the patient is probably better shown by exercise tolerance which may be influenced also by hemodynamic effects of the drug.

Thus Luxton et al. (12) showed that a nicotinic acid analogue with but minor vascular effects decreased post exercise ST depression in patients with angina pectoris. However they did not find any effect of the drug on exercise tolerance and ST depression during exercise was not reported on. If ST depression mirrors myocardial ischaemia it is surprising that Luxton et al. could not find any increase in exercise tolerance especially since both heart rate and BP during exercise factors of primary importance for myocardial oxygen consumption were lower with the drug. The influence on the exercise ECG or exercise tolerance may then have been due to other effects of the drug not related to those on lipid metabolism. The lack of significant effect on exercise tolerance may also be explained by the fact that both the evaluation of symptoms by the patient and the breaking point are rather subjective and factors such as general fatigue may well have contributed. It is probable that the exercise protocol in the present study with an almost continuous increase in load is more suitable to define the time of appearance of symptoms as well as the breaking point (2). In the present study plasma FFA lowering besides reducing ST depression at corresponding loads increased performance time to onset of chest pains by 7% although the improvement was barely significant. The smaller difference in absolute exercise time may as discussed above be due to the addition of general fatigue as a factor determining the breaking point.

The heart rate during exercise was slightly lower with than without the drug. This may have contributed to the improvement in ECG and exercise tolerance by the treatment. However although the systolic BP during exercise was the same with as without the drug immediately after work it was higher with treatment. It is therefore tempting to

conclude that the improved ECG reaction and exercise tolerance was the result of altered myocardial metabolism rather than an effect on the rate pressure product.

It is not evident why the heart rate was lower with the drug since if a vasodilatory effect had remained at the time of exercise an increased heart rate would have been the more likely result. It may have been the result of improved myocardial function with lower filling pressures (3) or less pain stimulation.

# ACKNOWLEDGEMENTS

This investigation was supported by grants from the Swedish Medical Research Council (04X-4494 and 19X-204).

# REFERENCES

- 1 Carlson L A & Örd L. The effect of nicotinic acid on the plasma free fatty acids. *Acta Med Scand* 172: 641, 1962.
- 2 Eklund B. Estimation of perceived pain during treadmill testing of patients with obliterative arterial disease of the lower limbs. *Wenner-Gren Center International symposium series* 28: 315. Pergamon Press, New York, 1977.
- 3 Engstedt L, Freyschuss U, Kaijser L & Åsén P. Hemodynamic findings in patients with intravascular red cell aggregation. *Acta Med Scand* (Suppl.) 472: 68, 1967.
- 4 Ho R J. Radiochemical assay of long-chain fatty acids using  $^{14}\text{C}$  as tracer. *Anal Biochem* 36: 105, 1970.
- 5 Kaijser L. Ekg förändringar vid coronarsufficiens. *En funktion av arbetsintensitet och duration*. *Läkarkartidningen* 63: 3340, 1966.
- 6 Kaijser L, Carlson L A, Eklund B, Nye E R, Rössner S & Wahlqvist M L. Substrate uptake by the ischemic human heart during angina induced by atrial pacing. In: *Effect of acute ischaemia on myocardial function* (ed M F Oliver, D G Julian & A W Donald), pp 223-233. Churchill Livingstone, Edinburgh and London, 1972.
- 7 Kaijser L, Eklund B, Olsson A G & Carlson L A. Comparative effects on plasma free fatty acid concentration and forearm blood flow of antilipolytic drugs. *Med Biol* 1: 111, 1973.
- 8 Hjekshus J A & Mun O D. Effect of fatty acids on myocardial function and heart rate in ischemic dog heart. *J Clin Invest* 51: 17, 1973.
- 9 —. Effect of inhibition of lipolysis on the experimental coronary artery occlusion. *Am J Physiol* 227: 1770, 1973.
- 10 Lassers B W, Kaijser L, Wahlqvist M L & Carlson L A. Release of plasma free fatty acids and myocardial metabolism of carbohydrate substrates. *Lancet* 1: 411, 1972.
- 11 Lassers B W, Wahlqvist M L, Kaijser L & Carlson L A. Effect of exercise and myocardial metabolism in man at rest and during rest. *Appl Physiol* 33: 77, 1972.
- 12 Luxton M R, Miller A E & Stone. Antilipolytic therapy in angina pectoris during exercise - induces ST segment depression. *Am J Physiol* 234: 1204, 1976.
- 13 Mjos O D. Effect of inhibition of lipolysis on myocardial oxygen consumption in the rat. *Isoproterenol*. *J Clin Invest* 45: 109, 1970.
- 14 Newsholme E A, Randle P J & Mjos O D. Inhibition of the phosphorylation of perfused rat heart by respiratory chain fatty acids and pyruvate. *Nature* 231: 109, 1970.
- 15 Robinson D F. Relation of heart rate and blood pressure to the onset of pain during exercise. *Circulation* 35: 1073, 1967.
- 16 Shipp S C, Opie L H & Chatterjee C K. Fatty acid and glucose metabolism in the perfused rat heart. *Nature* 189: 1018, 1961.
- 17 Svedmyr N, Harton L & Lindstedt L. Relationship between the plasma concentration of nicotinic acid and some of its pharmacological effects in man. *Clin Pharmacol Ther* 10: 411, 1961.
- 18 Wahlqvist M L, Kaijser L, Carlson L A, Carlson L A. Fatty acid as a myocardial substrate and oxygen restriction at rest and during prolonged exercise. *Am J Physiol* 227: 89, 1973.
- 19 Wahlqvist M L, Kaijser L, Carlson L A, Carlson L A & Carlson L A. The role of fatty acid hormones in the determination of myocardial metabolism in heart by fatty acid. *Am J Physiol* 234: 1204, 1976.

# Late Sudden Death after Surgical Correction of Coarctation of the Aorta

*Importance of Aneurysm of the Ascending Aorta*

Kolbjørn Forfang Hans Rostad Svein Sorland and Kjell Levorstad

*From Medical Department B Surgical Department A Pediatric Department  
and Department of Radiology University Hospital Rikshospitalet Oslo Norway*

ICT Follow up studies averaging 12 years  
ective surgery of 343 patients with coarcta  
ie aorta disclosed 38 late deaths, 16 of which  
iden unexpected and probably cardiovascu  
but two patients were normotensive post  
ely and in 4 of these the cause of death was  
dissecting aneurysm of ascending aorta In  
patient this aneurysm was repaired surgical  
13 other patients chest X ray had shown a  
ascending aorta before death At follow up  
nding aorta was dilated angiographically in 4  
t who had moderate systolic hypertension  
the valve disease The high incidence of  
n of ascending aorta in patients with coarcta  
probably due to hypertension during the  
etud, possibly in combination with congeni  
ness of the aortic wall, and to concomitant  
he lesion

Is coarctation of the aorta aneurysm of the  
aorta late sudden death  
Scand 206 375 1979

on the natural history of patients over 2  
age with coarctation of the aorta have re  
n average age at death of 34-35 years (2  
t review of 104 autopsied cases Reifen  
1 (11) reported sudden death in 29 patients  
of whom 19 (18.3%) died from rupture/  
n of the ascending aorta  
era for patients with coarctation of the  
ted in 1945 when Crafoord and Nylin (4)  
ed the surgical treatment However fol  
udies after surgical correction have shown  
e is still a considerable incidence of sudden  
10 13) The aims of the present work were  
the incidence and cause of late sudden  
er coarctectomy and to elucidate the role  
ism of the ascending aorta

## PATIENTS AND METHODS

Between 1948 and July 1973 356 patients 129 females and 227 males underwent surgical correction of coarctation of the aorta in our hospital (12) Eighteen patients were infants 120 1-12 years 154 13-29 years and 64 30 years of age or more There were 13 intra and postoperative deaths (3.7%) Ten of the dead patients were infants under 5 months of age and the other three were 32 36 and 40 years of age A follow up study of all 343 survivors was performed in 1975-77 During the follow up period of 2-28 years (mean 12) 38 late deaths had occurred a review of these will be published elsewhere (8 14) Information concerning causes of death were obtained from family doctors hospitals where the patients had been admitted near relatives and the Norwegian Central Bureau of Statistics

The present study comprises primarily 16 patients who died suddenly and unexpectedly within one hour after onset of symptoms (4.7% of the 343 survivors) Death from cerebral vascular accident (5 patients of whom at least 3 died from subarachnoid hemorrhage) was not included Four additional patients are included in whom aneurysm of ascending aorta was demonstrated at follow up the aortography being performed because hypertension was found Finally one patient is presented in whom aneurysm was found at the primary evaluation for coarctation of the aorta

## RESULTS

The pertinent data on the 16 late sudden cardiovascular deaths appear in Table I This part of the material was divided into 4 groups *Group 1* Four patients who died from proven dissection/rupture of aneurysm of ascending aorta They were all normotensive postoperatively and two had aortic valve disease Patient 3 was operated on for the dissection but he died on the 13th postoperative day In

Reprint requests to Dr K. Forfang Medical Dept B  
Rikshospitalet Oslo 1 Norway



Table 1 Data on 16 late deaths after coarctectomy (sudden unexpected death and aneurysm of ascending aorta)

AVD=Aortic valve disease AS=aortic stenosis AI=aortic insufficiency BAV=bicuspid aortic valve

Group	Pat no	Sex	Age (y)		Postoperative BP			AID
			At operation	At death	Years after operation	mmHg		
I	1	♂	9	27	8	130/80	-	
	2	♂	15	18	3	135/75	AS	4)
	3	♂	17	30	12	130/90	AI	
	4	♂	19	25	3	115/80	-	
II	5	♂	22	42	12	140/90	BAV	4)
III	6	♂	15	23	<1	130/80	-	
	7	♂	33	43	1	170/75	-	
	8	♂	48	58	9	170/100	-	
IV	9	♂	6	17	1	95/70	-	
	10	♂	13	14	1	130/80	AI	
	11	♂	16	23	6	135/90	-	4
	12	♂	24	25	-	-	-	
	13	♀	30	49	2	170/100	-	
	14	♂	31	47	2	150/80	-	
	15	♂	36	45	6	135/80	-	
	16	♂	50	54	-	-	AI	

patients 1 and 4 the aneurysm had ruptured into the pericardium. Histological examination of the ascending aorta was obtained from two patients (nos 3 and 4) and in both the media was thin with disruption of the few elastic fibres. Group II. One patient who had bicuspid aortic valve with insufficiency requiring valve replacement 12 years after coarctectomy.

Group III. In conjunction with the aortic valve surgery an aneurysm of ascending aorta was repaired with a graft. Group IV. Three patients who died suddenly and unexpectedly. All had before coarctectomy shown dilatation of the ascending aorta on chest X-ray giving a clue to rupture of the aorta as the cause of death. Group V. Eight patients who all died suddenly and there were no clues to the causes

of death. Only one of them (no 9) had aortic valve disease and the sole pathological finding was dilatation of the left ventricle. There was no significant dilatation at the site of coarctation. In two patients (nos 12 and 13) diastolic murmur was present before coarctectomy indicating aortic insufficiency. Moderate aortic insufficiency was found in one patient, whereas five of the others were almost normotensive.

The mean interval from the time of coarctectomy to death was 10 years (range 1-20) and 17% were under 40 years of age at death. All but one were males. The incidence of sudden death was 1.2% after operation on after 13 years of age and 1.6% in the younger patients (16%).

At follow up of the survivors -

Table II Data on 4 patients with aneurysm in ascending aorta detected at follow up

AVD=aortic valve disease R=resection DG=dacron graft I TFA=end to end anastomosis BAV=bicuspid aortic valve AI+=small aortic insufficiency AI++=large aortic insufficiency

Pat no	Sex	Age (y)		Operative technique	BP at follow up (mmHg)	Recurrent aortic regurgitation (mmHg)	AID
		At operation	At follow up				
17	♂	14	23	R DG I TFA	175/90	40	BAV
18	♂	14	23	R I TFA	155/100	40	BAV
19	♂	16	31	R I TFA	140/90	36	BAV
20	♀	29	45	IR	160/90	14	BAV



Aortography from patient 18 showing dilated aorta and a saccular aneurysm just below the left subclavian artery

The dilated aorta was found in four (Table II). They had bicuspid valves and three (nos 17, 19 and 20) had aortic insufficiency. Patient 20 had been previously treated for bacterial endocarditis 13 years after coarctectomy. A significant recoarctation was present in patients 17, 19. In patient 18 a dilated saccular aortic aneurysm with a diameter of 3 cm was found just distal to the site of coarctation (Fig 1). Fig 2 shows the aneurysm of the ascending aorta in patient 20. Fig 3 shows the dilatation of the ascending aorta in a 47-year-old man who recently underwent prior coarctectomy. BP was 170/100 mmHg. The pressure gradient across the coarctation was 20 mmHg and the aortic valve was bicuspid with mild regurgitation or stenosis.

## DISCUSSION

The present finding of a high prevalence of dilatation of the ascending aorta after surgical correction of coarctation of the aorta is remarkable as few such cases have been reported previously (6, 7, 10, 15, 16). Most of the present patients were normotensive postoperatively and a clinical diagnosis just prior to death would probably not

have predicted rupture of the aneurysm or sudden death from other causes. However, signs of aortic valve disease were present in 5 of the 16 patients. The present study has also shown a considerable overall incidence of late sudden death after coarctectomy (4.7%) during follow-up periods of 12 years on average. This is in good agreement with the report of Maron et al (10). A follow-up after 11–25 years of 194 patients revealed 23 (12%) late deaths, 22 of which were related to cardiovascular disease; the mean age at death was 35.1 years. Autopsy was performed in eight of the cases and rupture of aortic aneurysm was found in two. Death was sudden and unexpected in 11 of the 14 patients not autopsied. Ruptured major arterial vessel was probable in four of these patients and myocardial infarction in two others. In this material, non-survivors had experienced significantly longer periods of preoperative hypertension than survivors.

Simon and Zlot (13) studied 190 patients 1–15.5 years (mean 6.6) after operation. There were 11 late cardiovascular deaths; the mean age at death being 32.5 years. Five patients died suddenly and autopsy



Fig 2 Aortography from patient 20 showing aneurysm of the ascending aorta



Fig 3 Dilatation of the ascending aorta in a 19-year-old man with unoperated coarctation of the aorta

was performed in only two. Dissecting aortic aneurysm was found in one.

In their classical review, Peifenstein et al (11) reported dissection of the ascending aorta in 1837 patients dying with the coarctation; their mean being 30 years. It is therefore not surprising that some of the preformed aneurysms in the course of time will rupture even after normalization of the BP by coarctectomy.

Broden and Karrell (1) studied 123 cases by aortography before coarctectomy and frequently found dilatation of the ascending aorta; the dilatation sometimes being so severe that the vessel was saccular. They also made a comparison between the mean width of the ascending aorta in coarctation and the corresponding values in normal cases. The results indicated that in coarctation the ascending aorta was wider than normal even in the first decade of life and that this difference increased with age. The cause of the dilatation of the ascending aorta in patients with coarctation is not yet clarified. Congenital thinning and medial changes due to hypertension or other factors have been discussed (11). However, hypertension during

the growth period is probably of great importance, but a contribution from congenital weakness of the aortic wall cannot be excluded. Histologic microscopic studies can solve this question. In accordance with the findings reported by White et al (12) indicating that the pathogenesis of the congenital aortic aneurysm may also be of importance in the process emphasized by Edwards (6), aortic aneurysms leading to bicuspid aortic valves may lead to a significant laceration of the ascending aorta. This may lead to classical dissecting aortic aneurysm or localized saccular aneurysm.

The incidence of sudden death was high in patients operated on after puberty or in children. This finding might be due to the intense hypertensive stress on the aorta. The shorter the younger the patient, the greater the aneurysm. On the other hand, only a few patients followed more than 20–25 years after coarctectomy in childhood.

The present follow-up study led to the discovery of aortic aneurysms in 4 patients with mainly systolic hypertension. All had aortic disease and 3 had re-coarctation with a gradient of  $\geq 40$  mmHg or more. In these cases a lesion of the aortic wall may have caused the formation of aneurysm. Fredelius and I have described a spindle-shaped dilatation of the ascending aorta in 8 out of 37 patients who went aortography after coarctectomy. This was interpreted as a sign of aortic aneurysm if pressure gradients were not measured. In a series of postoperative aortographies this was reported in the literature.

Pregnancy in women with unoperated coarctation of the aorta implies a risk of rupture of the aorta. The main danger is dilatation of the ascending aorta. This danger will probably increase after coarctectomy in women with aneurysm of the ascending aorta.

As previously emphasized by many, there is a need for close postoperative follow-up after surgical correction of coarctation and aortic valve disease may progress and sometimes lead to laceration of the ascending aorta. Overall there is a considerable risk for aortic aneurysm some years after surgery. It is highest in patients with preoperative aneurysm, even moderate systolic hypertension.

for surgery in childhood using a thorough technique and leaving no residual pressure at the site of coarctation

## REFERENCES

1. B & Karnell J Coarctation of the aorta. Angiographic studies before and after operation. *Acta Chir Scand* 165 1958
2. Bell J Natural history of coarctation of the aorta. *Heart* 32 633 1970
3. M D Coarctation of the aorta. *Med Clin N Am* 61 665 1977
4. Ford C & Nylan G Congenital coarctation of aorta and its surgical treatment. *J Thorac Surg* 30 1945
5. K & Woolly C F Coarctation of the aorta and its surgical treatment. *Ann Intern Med* 78 706 1973
6. J E Aneurysms of the thoracic aorta complicating coarctation. *Circulation* 47 195 1973
7. J E Carey L S Neufeld H N & R G Congenital heart disease vol 2 p 687. Lea Philadelphia 1965
8. K Rostad H & Sorland S Coarctation of aorta. A follow-up study of 218 patients operated for 13 years of age. In *Acta Med Scand (Suppl)* In press 1979
9. Eken T & Jagt T Roentgen signs of aortic valvular stenosis in aortographic follow up studies of patients treated surgically for coarctation of the aorta. *Acta Chir Scand* 127 243 1964
10. Maron B J Humphries J O Rowe R D & Melits E D Prognosis of surgically corrected coarctation of the aorta. A 20-year postoperative appraisal. *Circulation* 47 119 1973
11. Reifenshtein G H Levine S A & Gross R E Coarctation of the aorta. A review of 104 autopsied cases of the adult type. 2 years of age or older. *Am Heart J* 33 146 1947
12. Rostad H Sorland S & Forfang K Coarctation of the aorta. A review of 356 operated cases. *Vasc Surg* 13 22 1979
13. Simon A B & Zlot A E Coarctation of the aorta. Longitudinal assessment of operated patients. *Circulation* 50 456 1974
14. Sorland S Rostad H & Forfang K Coarctation of the aorta. A follow up study of 138 patients operated on in infancy or childhood. *Acta Paediatr Scand* In press 1979
15. Villagra F Rusilanchas J J Tellez G Maronas J M Iglesias A & Aymerich D F Early and late death of surgically treated patients with coarctation of the aorta. *Vasc Surg* 11 63 1977
16. White C W & Zoller R P Left aortic dissection following repair of coarctation of the aorta. The contribution of abnormal hemodynamics to medial degeneration. *Chest* 63 573 1973

# The very journals for you!

## **Acta Chirurgica Scandinavica**

Editor L. Thorén

8 issues per volume Free supplements Including free subscriptions to the *Scandinavian Journal of Plastic and Reconstructive Surgery* (without suppl) the *Scandinavian Journal of Thoracic and Cardiovascular Surgery* (without suppl) and the *Scandinavian Journal of Urology and Nephrology* (without suppl) Together 17 issues per year

Current volume 145/1979

Sw kr 420 per year incl postage

## **Acta Dermato-Venereologica**

Editor Nils Thyresson

6 issues per volume Free supplements

Current volume 59/1979

Sw kr 190 per year incl postage

## **Acta Medica Scandinavica**

Editor J Waldenström

6 issues per volume Free supplements

Current volumes 205-206/1979

Sw kr 375 per year (two volumes) incl postage

## **Acta Oto-Laryngologica**

Editor C A Hamberger

6 issues per volume Free supplements

Current volumes 87-88/1979

Sw kr 300 per year (two volumes) incl postage

## **Pædiatrisc Scandinavica**

Editor R Zetterström

6 issues per volume Free supplements

Current volume 68/1979

Sw kr 300 per year incl postage

## **Scandinavian Audiology**

Editor Stig Arlinger

4 issues per volume Free supplements

Current volume 8/1979

Sw kr 175 per year incl postage

## **Scandinavian Journal of Infectious Diseases**

Editors Justus Ström and Sten Wanhåll

4 issues per volume Free supplements

Current volume 11/1979

Sw kr 175 per year incl postage

## **Scandinavian Journal of Plastic and Reconstructive Surgery**

Editor Bengt Johanson

3 issues per volume Free supplements

Current volume 13/1979

Sw kr 185 per year incl postage

## **Scandinavian Journal of Psych**

Editor Lars Kieboen

4 issues per volume

Current volume 20/1979

Sw kr 170 per year incl postage

## **Scandinavian Journal of Rehabilitation Medicine**

Editor Olof Håk

4 issues per volume Free supplements

Current volume 11/1979

Sw kr 150 per year incl postage

## **Scandinavian Journal of Rheumatology**

Editor Veikko Laine

4 issues per volume Free supplements

Current volume 8/1979

Sw kr 150 per year incl postage

## **Scandinavian Journal of Social Medicine**

Editor Ragnar Bergholm

3 issues per volume Free supplements

Current volume 7/1979

Sw kr 140 per year incl postage

## **Scandinavian Journal of Thoracic and Cardiovascular Surgery**

Editor Viking Oyv Borch

3 issues per volume Free supplements

Current volume 13/1979

Sw kr 185 per year incl postage

## **Scandinavian Journal of Urology and Nephrology**

Editor Åke Frim

3 issues per volume Free supplements

Current volume 11/1979

Sw kr 185 per year incl postage

## **Uppsala Journal of Medical Sciences**

Editor Gunnar Agren

3 issues per volume Free supplements

Current volume 21/1979

Sw kr 100 per year incl postage

Swedish subscribers Add V A T to all prices

Free inspection copies on request—write to

**The Almqvist & Wiksell Periodical Com**  
Box 62, S-101 20 Stockholm

# Oesophageal Symptoms and Manometry in Valvular Heart Disease

Lars Tibblin and Bengt Wernberg

From the Departments of Otolaryngology and Clinical Physiology  
Lundberg Hospital, Luleå, Sweden

CT A possible relationship between heart oesophageal dysfunction (OD) and symptoms was studied in 47 patients with valvular disease. They were investigated with oesophagometry and oesophageal acid perfusion. It was found in 32% of the patients. A local increase in the middle part of the oesophagus was an effect of cardiac enlargement and not of the oesophagus was found at manometry. The incidence of OD and of oesophageal symptoms was the same in patients with and without oesophageal compression. We did not find evidence that valvular disease in itself provokes the symptoms of chest pain and cough in patients with valvular heart disease are due to OD.

Oesophageal dysfunction, valvular heart disease.  
Scand J Clin Lab Invest 1979

previously found a high incidence of oesophageal dysfunction (OD) in patients with proved or proven coronary heart disease (8, 9). Patients observed in a coronary care unit with symptoms of chest pain (2). Our survey of the interrelationship between OD and heart disease is confirmed by data on patients with valvular heart

symptoms of valvular heart disease vary in type and severity of the lesion. Two of the symptoms may be chest pain and cough. Since both symptoms in patients with OD (2, 10) symptoms found in valvular heart disease could be due to secondary to mechanical influence of the enlargement on the oesophagus. The aim was therefore to estimate the incidence of OD in a group of patients with a well defined chronic valvular heart

## PATIENTS AND METHODS

The study comprises 26 male (mean age 69 years, range 57-71) and 21 female patients (mean age 68 years, range 43-89) referred to the Cardiology Unit for preoperative heart catheterization. Twenty-three patients had aortic, 9 mitral and 15 both aortic and mitral valvular disease. Six of the patients were classified as belonging to function group I according to the NYHA, 19 to group II and 22 to group III.

Besides the cardiac investigations, which included right and left heart catheterization, left ventricular angiography and thoracic aortography, an oesophageal manometry and an oesophageal acid perfusion test were performed. The patients also filled in a questionnaire regarding symptoms of possible oesophageal or cardiac origin (6, 7). Oesophageal symptoms such as globus sensation, dysphagia and chest pain were given point scores and an oesophageal symptom score was calculated for each patient. The symptom score was slightly modified after Spindow et al. (1).

Sphincter tone, sphincter displacement, gastro-oesophageal reflux, oesophageal tone and motility by swallowing were investigated at the oesophageal manometry (2). The acid perfusion test was slightly modified from the original Bernstein test (1, 3).

OD was considered to be present if at least one of the following criteria was met: 1) Positive acid perfusion test. 2) Manometrically verified hiatal hernia with a length of 2 cm or more. 3) Dysmotility in combination with hypotension of the lower oesophageal sphincter (LES) or reflux. 4) Severe dysmotility, i.e. segmental contractions by swallows at 3 or more of 10 different levels in the oesophagus. Hypotension of the LES or gastro-oesophageal reflux as a single finding or a local pressure increase in the middle part of the oesophagus were not classified as OD.

Heart volume was calculated according to Jonzell (4) from chest X-rays taken in the standing position.

Fisher's exact test, Wilcoxon's rank sum test and Student's *t* test for unpaired data were used for statistical analysis.

Abbreviations: OD = oesophageal dysfunction, LES = lower oesophageal sphincter.

Table 1 Outcome of oesophageal function tests

M=mitral valvular disease A=aortic valvular disease

	M (n=9)	A (n=23)	M+A (n=32)
Hernia	0	5	2
Dysmotility	4	5	4
LES incompetence	5	11	3
Positive acid perfusion test	1	3	4
OD	3	7	5

## RESULTS

OD was found in 32% of the patients (Table 1). The incidence of OD did not differ between the three groups of valvular disease. The patients with OD had an increased frequency of heart burn, acid regurgitation, globus sensation and surfeitiness after meals (Table 1). A history of chest pain was presented by 62% of the patients and 36% complained of cough, but the difference in incidence between patients with or without OD was insignificant. The rank sum of oesophagus related symptoms was 478 for the 15 patients with OD and 701 for the 32 with normal oesophageal function ( $p < 0.01$ ). Patients with aortic valvular disease alone had more often chest pain (74%) than patients with mitral valvular disease alone (22%) ( $p < 0.02$ ). All patients who pre-

Table 2 Symptoms given in the oesophageal questionnaire in relation to objective findings in 15 with and 32 without OD

	OD (%)	Non-OD (%)
Do you often have heart burn?	13	0
Do you often have acid regurgitations?	33	9
Do you often feel a lump in your throat?	33	13
Do you often feel surfeited after a meal?	40	13
Do you often have a hacking cough?	40	34
Do you sometimes have chest pain?	67	59
Does your chest pain improve when lying with your head raised?	27	25
Do you sometimes wake up at night because of chest pain?	33	24
Do you sometimes get chest pain in cold environments?	20	44
Do you get chest pain with emotional distress?	33	53
Does your chest pain get worse in connection with exertion?	67	46
Effort angina at exercise test	13	9

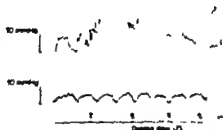


Fig. 1 Pressure registration from the lower oesophagus in a patient with combined mitral and aortic valvular disease (upper) and in a patient with aortic valvular disease (lower). The irregular pressure in the lower registration is due to atrial fibrillation.

sented typical effort angina at the time of aortic valvular disease.

A local pressure increase of 0.1 mmHg (range 3-15) in the middle part of the esophagus was found at manometry in 10% of the patients. The mean length of the zone of increase was 5.3 cm and it was located on average 6.5 cm above the LES. Local pressure increase, pressure variations and pressure waves were sometimes superimposed on the contractions (Fig. 1). These pressure variations resembled atrial pressure variations and had a similar frequency to the heart rate in patients with sinus rhythm and occurred with atrial fibrillation.

There was no difference in incidence between the group of patients with local pressure increase (5/18) and the group without (10/29). Neither was there any difference in oesophageally related symptoms between the two groups. There was no overrepresentation of patients with mitral stenosis or mitral regurgitation with local pressure increase in the oesophagus. The mean roentgenological heart volume was (S.F.M.) ml/m BSA for the group with local pressure increase and 646±32 for the group without (p>0.05).

## DISCUSSION

An increase in pressure within the oesophagus was observed in more than one third of the patients. There was no relation between heart size on x-ray and pressure increase as determined by manometry in accordance with observations by Helmsen (11). This is partly explained by the fact that x-ray pictures do not indicate the size of separate heart chambers but only the size of the total silhouette of the heart.

to have enlarged left atria there was no representation of local pressure increase in the aorta. Therefore other factors such as the position of thoracic spine and the cardiac/aortic retro-posterior distance ratio may be of value but were not evaluated here. With the observed pressure increase within the oesophagus is low compared to the magnitude of pressure increase induced by swallowing it is possible to OD and oesophageal symptoms. We previously found that more than 40% of patients with chest pain have signs of OD (7, 8, 9). Schel and Paulsen (10) reported that one of their patients with hiatal hernia or reflux of bronchitis. Among our patients 62% had chest pain and 36% cough. The question therefore is if chest pain and cough in patients with heart disease are due to an overrepresentation of OD provoked by cardiac enlargement. The incidence of OD however was only 32% among patients and the frequency of chest pain or cough did not differ significantly between those with and without OD. Therefore it does not seem that symptoms of chest pain and cough in patients with valvular heart disease are caused by cardiac enlargement. We find any indications that a valvular heart disease provokes OD. The incidence of OD was similar in patients with and without local pressure increase in the aorta.

## REFERENCES

1. Areskog M, Tibblin L & Wranne B. Oesophageal acid perfusion test as a complement to work test in patients with chest pain. *Acta Med Scand* 201: 449, 1977.
2. —. Oesophageal dysfunction in non-infarction coronary care unit patients. *Acta Med Scand* 205: 279, 1979.
3. Bernstein L M & Baker L A. A clinical test for oesophagitis. *Gastroenterology* 34: 60, 1968.
4. Jonsell S. A method for the determination of the heart size by teleroentgenography (a heart volume index). *Acta Radiol* 30: 325, 1939.
5. New York Heart Association. Diseases of the heart and blood vessels. 6th ed. Little Brown & Co. Boston, 1964.
6. Rose G A. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull WHO* 27: 645, 1962.
7. Spandow O, Sökyer H & Tibblin L. Function of the lower oesophageal sphincter in a population selected at random. A manometric, radiological and questionnaire study. *Acta Otolaryngol* 78: 294, 1974.
8. Svensson O, Stenroos G, Tibblin L & Wranne B. Oesophageal function and coronary angiogram in patients with disabling chest pain. *Acta Med Scand* 204: 173, 1978.
9. Tibblin L & Wranne B. Oesophageal dysfunction in male patients with angina-like pain. *Acta Med Scand* 200: 391, 1976.
10. Urschel H C & Paulsen D L. Gastroesophageal reflux and hiatal hernia. Complications and therapy. *J Thorac Cardiovasc Surg* 53: 71, 1967.
11. Wilhelmsen L. Lung mechanics in rheumatic valvular heart disease. *Acta Med Scand (Suppl)*: 489, 1968.

## ACKNOWLEDGEMENTS

Supported by grants from the Swedish Medical Research Council (17X-4/60) and from the Swedish National Association Against Heart and Chest Diseases.



— 27 —

4

# Disopyramide Plasma Levels in Cardiac Patients on Maintenance Therapy

Knud Landmark, Liv Storstein and Anne Larsen

From Medical Department B, Rikshospitalet, University of Oslo, Oslo, Norway

The antiarrhythmic agent disopyramide (dosage of 200 mg/8 h) was given to 7 cardiac patients. The drug was fairly rapidly absorbed and peak plasma concentration ( $3.5 \mu\text{g/ml}$ ) was 1 h after administration of the first dose. Mean biological half-life ( $7.8 \text{ h}$ ) was slightly lower than that reported in normal volunteers. Mean steady state plasma concentrations in the therapeutic range were attained 24 h after start of medication. The fluctuations in plasma levels were in the order of 30% however, and the values were observed. The drug was tolerated.

Disopyramide cardiac patients absorption  
dosage interval.  
Scand J Clin Lab Invest 1979

Disopyramide (4-dimethylamino-2-phenyl-2-methyl-5-pyrimidinol) is pharmacologically related to other drugs such as quinidine and procainamide. The drug reduces the incidence of ventricular arrhythmias (4, 5) and it has been shown to be a safe and effective agent in the prevention of potentially serious arrhythmias following myocardial infarction (9). The drug is also effective in maintaining sinus rhythm in patients after electroconversion of atrial fibrillation (6).

Plasma levels between 2 and  $4 \mu\text{g/ml}$  are considered to be required for optimal antiarrhythmic effect (13, 14). Deano et al. (4) have demonstrated that a bolus of 2 mg/kg of disopyramide followed by continuous intravenous drip infusion caused a marked reduction in frequency of premature contractions. This effect correlated to serum levels of approximately  $2.5 \mu\text{g/ml}$ .

Side-effects of disopyramide are primarily related to its anticholinergic action and they consist mainly of dry mouth, blurred vision and in patients with hypertrophy of the prostate urinary hesitancy may occur (8, 14).

Cardiac and renal failure may influence the absorption, distribution, metabolism and elimination of several cardioactive drugs including disopyramide (2, 15, 17, 18) and delay the attainment of steady state plasma concentration ( $C_{ss}$ ). Adjustment of the dose according to the plasma concentration will however allow optimal treatment of patients with renal failure or low cardiac output states. In the present study we have measured steady state levels of disopyramide in cardiac patients and present further clinical evidence that adequate maintenance therapy is possible at a fixed dosage interval slightly longer than that recommended to healthy human volunteers (18).

## PATIENTS AND METHODS

Seven patients with heart disease participated in the study. Informed consent had been obtained from all. Their age, diagnosis, physical characteristics and haemodynamic parameters are shown in Table 1. Clinical and haematological examination revealed otherwise no abnormalities. The renal function which was assessed by serum creatinine measurements was slightly impaired in patient 2 ( $170 \mu\text{mol/l}$ ). Most of the patients were subjected to continuous ECG monitoring in a coronary care unit throughout the investigation period. Six patients had ventricular premature contractions not requiring adequate antiarrhythmic therapy, one patient had paroxysmal atrial fibrillation. A left heart catheterization with ventricular and selective coronary angiography was performed in 5 patients.

Abbreviations:  $t_{1/2}$  = biological half-life;  $k_{el}$  = elimination rate constant;  $FCG$  = electrocardiographic;  $C_{ss}$  = steady state plasma concentration.

Table I Details of the patients

LVEDP=end diastolic pressure of the left ventricle CM=cardiomyopathy MI=myocardial infarction VPC=ventricular premature contractions PAF=paroxysmal atrial fibrillation LV=left ventricle (over 100 ml)

Patient no	Age (y)	Sex	Diagnosis	Arrhythmia	Heart size (rel. volume)	LVEDP (mmHg)	Diagnosis	Angiography
1	34	♂	CM	VPC	545	14	+	Red coronary arteries LV normal size
2	63	♂	MI	VPC	420	11	+	LV dilated coronary arteries
3	48	♂	MI	VPC	460	13	-	LV aneurysmal by lateral coronary artery disease
4	58	♂	MI	VPC	625	25	+	LV dilated by infarction in anterior region
5	78	♀	MI	VPC	610		+	
6	50	♂	MI	VPC	390	18	-	LV aneurysmal by infarction
7	67	♀	MI	PAF	440		+	

Table II Individual and mean plasma concentrations of disopyramide ( $\mu\text{g/ml}$ )

Patient no	Disopyramide 200 mg	Hours after the start of disopyramide medication							Disopyramide 200 mg	9	13	17
		1	1	2	4	6	8					
1		0.4	2.4	3.2	2.5	2.2	1.7		1.7	2.1	2.1	2.1
2		0	3.6	2.7	2.8	2.1	2.2		1.8	2.1	2.1	2.1
3		1.9	4.7	4.3	3.9	3.2	2.8		3.2	2.1	2.1	2.1
4			2.7	2.3	1.5	1.3	1.3		2.4	2.1	2.1	2.1
5							1.8		2.3	2.1	2.1	2.1
6		4.4	5.4	5.1	3.4		2.1		4.0	3.9	3.9	3.9
7		0.5	2.1	2.9	2.5	2.1	2.2		2.5	2.1	2.1	2.1
Mean		1.8	3.5	3.4	2.8	2.2	2.0		2.6	2.4	2.4	2.4
SD		2.1	1.3	1.1	0.8	0.7	0.5		0.8	0.9	0.9	0.9

First dose given at 8 a.m.

#### Drug administration schedule

Disopyramide (Durbin®) 200 mg was given at 8-hour intervals initially at 8 a.m. in the fasting state and then at 8, 16, 24, 32, 40, 48, 56, 64 and 72 h after the start of the investigation.

#### Blood samples and disopyramide assay

Blood samples (10 ml) into lithium heparin anticoagulants were drawn through an indwelling Venflon® cannula inserted into an antecubital vein at 30 min and at 1, 2, 4, 6, 8, 9, 10, 12, 14, 24, 25, 26, 32, 33, 34, 48, 49, 57 and 74 h after the first dose. After centrifugation plasma was stored at  $-20^\circ\text{C}$  in plastic tubes until analysed. Estimation of the plasma concentration of disopyramide was carried out at the Roussel Laboratories, Sweden, by a gas liquid chromatographic method using a 3% OV-17 column (2).

Table III Plasma concentration of disopyramide at various times after the start of the investigation

Patient no	Time (h)	Conc. ( $\mu\text{g/ml}$ )
1	4	0.4
2	9.0	0.5
3	9.4	0.5
4	9.0	0.5
5		
6	8.0	0.5
7	9.4	0.5
Mean	8	0.5
SD	1.9	0.5

IV Individual and mean plasma concentrations of d sopyramide ( $\mu\text{g/ml}$ )

Disopyramide 200 mg	Hours after the start of d sopyram de medication							Diff between max and min values (%)
	24	25	26	D sopyram de 200 mg	31	33	34	
	24	24	30		24	25	34	47
	36	77	91		40	50	55	38
	30	69	53			27	40	
		17	39		19	36	13	30
	37	33			32	31	45	40
	23	38	45		26	27	36	38
	27	79	37		24	35	38	58
	29	40	49		28	37	37	31
	05	22	22		07	09	13	31

## RESULTS

Disopyramide given at 7 a.m. on the first day was absorbed rapidly and the highest mean plasma concentration ( $3.5 \pm 1.3 \mu\text{g/ml}$ ) was measured 1 h after administration (Table II). The drug was eliminated from the blood with a mean biological half life ( $t_{1/2}$ ) of 1.9 h (range 0.5-9.5) (Table III). The individual values were derived from the semilog plasma concentrations vs time plots for the first dose (Table II). The mean elimination constant ( $k$ ) was  $0.095 \pm 0.077 \text{ h}^{-1}$  ( $0.138-0.073$ ) (Table III). The second administration at 3 p.m. (approximately 1.5 h after intake of food) produced a lesser increase in mean plasma concentration and the drug was eliminated at a slower rate (Table II). The mean plasma concentration was defined as the concentration of d sopyramide at each dose at 4-37 h after administration of the first

dose. The mean minimum plasma concentration was approximately  $3 \mu\text{g/ml}$  and remained at that level throughout the rest of the study (Tables IV and V). The mean difference between the minimum and maximum plasma concentrations (determined 2 h after intake of d sopyramide) was approximately 30% at steady state plasma levels; however, there was a wide spread of the values observed (Tables IV and V).

The drug caused slight anticholinergic effects in some patients but was otherwise well tolerated.

## DISCUSSION

This study demonstrates that disopyramide given to cardiac patients in fasting state was absorbed fairly rapidly from the gastrointestinal tract and peak plasma levels assumed to be within the therapeutic range were attained 1-2 h in all and maintained

V Individual and mean plasma concentrations of disopyramide ( $\mu\text{g/ml}$ )

Disopyramide 200 mg	Hours after the start of d sopyram de medication							Diff between max and min values (%)
	48	50	Diff between max and min values (%)	D sopyram de 200 mg	72	74		
	21				22			
	46				47			
	38	49	30		44	50	14	
	35	53	51		41	48	17	
	21	20	5		22	30	37	
	30	46	53		29	40	38	
	26	30	15		23	39	70	
	31	40	29		32	41	35	
	09	14	25		11	08	21	

in most patients for at least 8 h after the first dose. The peak plasma concentrations correspond well to those found by Whiting and Miller (18) in healthy volunteers. On the other hand the values are considerably higher than those observed by others in normal subjects (3). Ward and Kinghorn (17) found that the most striking difference between patients and healthy volunteers after identical oral doses was the much lower plasma concentration profile observed in the former. In patients with heart failure the absorption of quimidine and procainamide is often delayed (1, 12). The reason for these discrepancies is not obvious. The reduced and apparently delayed absorption—and the slower elimination associated with the second dosage (given 8 h after the start of the medication)—is probably related to intake of food which delays gastric emptying. Disopyramide is a weak base ( $pK_a$  9.2) and the absorption will therefore take place in the gut.

Disopyramide is predominantly (40–60% of the dose) eliminated by renal excretion of the unchanged drug, 15–20% as the mono-N-dealkylated metabolite (11). It has been shown that  $t_{1/2}$  was not appreciably affected down to a creatinine clearance of 60 ml/min<sup>-1</sup>. The mean  $t_{1/2}$  of 7.8 h and the mean  $k_{el}$  of 0.093 h<sup>-1</sup> found in this investigation are in accordance with values previously found in cardiac patients (15–17). In healthy volunteers the reported values for  $t_{1/2}$  and  $k_{el}$  were within the ranges of 4–6.0 h and 0.110–0.173 h<sup>-1</sup> respectively (11, 15, 18). The altered elimination characteristics for disopyramide observed in cardiac patients may be related to impaired hepatic metabolism and/or reduced renal excretion secondary to cardiac failure (2).

When a drug is administered orally the desired  $C_{ss}$  is achieved after 4–5  $t_{1/2}$ . In the present study a mean  $C_{ss}$  within the therapeutic range was attained 24–32 h after the start of medication. The mean fluctuations in the  $C_{ss}$  were in the order of approximately 30%.

In healthy volunteers Whiting and Miller (18) have assumed that substitution of relevant mean kinetic parameters into the formula of Wagner et al. (16) and a  $C_{ss}$  of 3.5 µg/ml would necessitate an oral dose of 200 mg, 6 h.

$$\text{Dose} = \frac{A_{ss} \times V_d \times T \times C_{ss}}{f}$$

where  $V_d$  = volume of distribution,  $T$  = dose interval,  $f$  = bioavailability.

In most of our patients  $A_{ss}$  was probably reduced (15–17) because  $t_{1/2}$  had to be increased. In patients with heart failure associated with low renal states recommendations for disopyramide cannot be derived from normal values. Close monitoring of plasma disopyramide concentrations will however allow an adjustment to be made and is therefore essential.

Except for slight symptoms such as dry mouth and tacholinergic effect of disopyramide, it was well tolerated by our patients.

## REFERENCES

1. Bellet S, Roman L, Rabinowitz A. The effect of disopyramide on the heart rate and rhythm in normal subjects and patients with heart failure and renal insufficiency. *Am J Cardiol* 27: 468, 1971.
2. Benowitz N, L. & Menon N. Pharmacokinetics of disopyramide in patients with cardiac failure. *Clin Pharmacol Ther* 1: 389, 1976.
3. Bryson S, M., Whiting B. & Laver G. The pharmacokinetics of disopyramide serum and pharmacokinetics of disopyramide applied to the assessment of bioavailability. *J Pharm Med* 6: 409, 1973.
4. Deano D, A., Wu D, M., Miller R. & Lee H. Efficacy of disopyramide in the treatment of atrial fibrillation. *Am J Cardiol* 37: 100, 1976.
5. Hayler A. M. & Flanagan R. J. A study of the pharmacokinetics of disopyramide in patients with heart failure. *Chromatographia* 11: 461, 1978.
6. Hantel G., Louch A. & Koenig W. The effect of disopyramide on the heart rate and rhythm in patients with atrial fibrillation after electrical conversion. *Am J Cardiol* 35: 151, 1975.
7. Hurling B. & Rosenbaum G. A study of the haemodynamic effects of disopyramide in patients with atrial fibrillation. *Am J Cardiol* 37: 100, 1976.
8. — Haemodynamic and electrocardiographic effects of disopyramide in patients with atrial fibrillation. *Am J Cardiol* 37: 100, 1976.
9. Jones M. H., Jones D. G., Jones M. F., Jones P. B., Jones F. M. & Jones P. J. Disopyramide in prophylaxis of atrial fibrillation. *Am J Cardiol* 37: 100, 1976.
10. Jones M. H. & Jones D. G. The use of disopyramide in the treatment of atrial fibrillation. *Am J Cardiol* 37: 100, 1976.
11. Karmali M. A. The pharmacokinetics of disopyramide. *Am J Cardiol* 37: 100, 1976.
12. Karmali M. A. The pharmacokinetics of disopyramide. *Am J Cardiol* 37: 100, 1976.
13. Muggia H. E. A study of the pharmacokinetics of disopyramide in patients with heart failure. *Am J Cardiol* 37: 100, 1976.

- cho A P Disopyram de Serum level and arrhythmia con ers on Am Heart J 92 57 1976
- go R E Warn ca W Og lvie R J Kreeft J indjer E Correlat on of d sopyram de pharmacodynamics w h efficacy in ventricular tachyarrhythmia. J Int Med Res (Suppl) 1 54 1976
- ser J G Northolm J I Alway C D & Carer O S Blood levels of drugs at the equilibrium after multiple dos ng Nature 207 1301 1965
- l J W & Kinghorn G R The pharmacokinetics of disopyram de following myocardial infarct on: special reference to oral and intravenous dose rates J Int Med Res (Suppl) 1 49 1976
- 18 Wh t ng B & M ller S Disopyram de pharmacokinetics: Relationship to bioavailability and renal impairment In Proceedings of the Disopyram de (Rhythmolan) Seminar held n the School of Pythagoras St Johns College Cambridge March 24th & 25th 1977 (ed S J Anker & D F Wood ngs) p 11
- 19 Zainal N Carmichael D J S Griffiths J W Besterman E M M k dner P H G lham A D & Summers G D Oral disopyram de for the prevention of arrhythmia in patients w th acute myocardial infarct on admitted to open wards Lancet 2 887 1977

)

# Reduced Vibratory Perception and Corneal Sensitivity and Metabolic Disturbances Following Intestinal Bypass Surgery

H Hey N Vest Nielsen B Lund Bj Lund and O H Sørensen

From the Departments of Medicine and Ophthalmology Næstved County Hospital Næstved, the Department of Medicine D Frederiksberg University Hospital Copenhagen, the Department of Orthopaedic Surgery Frederiksberg County Hospital Hillerød and Department of Medicine F Herlev University Hospital Copenhagen Denmark

ACT Decreased corneal sensitivity and vibratory perception suggesting a diagnosis of polyneuropathy were demonstrated in some of 26 patients who had undergone intestinal bypass surgery. Psychological tests revealed signs of disturbance of the autonomic nervous system. A deficiency of 25-hydroxyvitamin D was demonstrated, clearly related to the frequency of stools and to the weight loss. This deficiency might play a role in the pathogenesis of the polyneuropathy.

polyneuropathy corneal sensitivity vibratory perception 25-hydroxyvitamin D obesity jejunoileal bypass

and 706 391 1979

In the last decade intestinal bypass surgery has been used as a treatment for massive obesity. One of the complications reported (1-4, 5, 7, 8, 10, 12, 21, 22) is a polyneuropathy for which several possible causes (11) have been suggested. The aim of this study was to investigate the presence of polyneuropathy by assessing the corneal sensitivity and vibratory perception in bypass patients and in controls and comparing the results with various biological and psychological

## SUBJECTS AND METHODS

The study included 26 patients aged 20-57 years (mean 35) who had undergone surgery for severe obesity between Nov. 1969 and Dec. 1976. All were included in the study. All had given their informed consent to the investigation. An end-to-side jejunum-preserving 50 cm of the small intestine was removed in all. The jejunum/ileum ratio varied from 37.5 cm of jejunum and 12.5 cm of ileum to 50 cm of jejunum and 12.5 cm of ileum. The mean period since surgery was 8 months at the time of the investigation.

The control group comprised 21 members of the local blood donor group aged 18-47 years (mean 32).

The bypass-operated patients were on an uncontrolled diet and were routinely given multivitamin tablets containing 1200 IU of vitamin D<sub>3</sub>. Most of the patients received other supplements such as calcium, magnesium, potassium, folic acid and cobalamin.

Patients and controls were excluded from the study if they had corneal disorders or had undergone eye surgery, were using eyedrops or contact lenses, had a history of either neurological or arteriosclerotic diseases or took psychopharmacological drugs or excessive amounts of alcohol.

The corneal sensitivity and vibratory perception were measured without knowing whether the subjects were patients or controls. The corneal sensitivity was tested using Cochet and Bonnet's aesthesiometer with a nylon filament with a diameter of 0.12 mm (6). By changing the length of the filament (0-60 mm) the cornea could be stimulated with different loads. The centre of the cornea was chosen for application of the stimulus as described elsewhere (6, 18). The results of three stimuli were recorded for each eye and the mean was used in the final analyses.

The vibratory perception was registered on the pulps of the index fingers (IF) and on the great toes (GT) using a bioaesthesiometer (Bio-Medical Instrument Company Chagrin Falls, Ohio) (17, 18). The threshold value for the vibratory perception was read directly from a voltmeter which indicated the amplitude of the applied vibrations. Three consecutive measurements of the threshold value on both extremities in lying position were recorded and the mean values were used in the final calculations.

Blood samples were taken with the subjects in fasting state. Serum calcium, potassium, inorganic phosphate and alkaline phosphatase were measured on an SMA 12/60 autoanalyser. Serum folic acid and vitamin B<sub>12</sub> were measured by microbiological assays. Serum 25-hydroxyvitamin D (25-OHD) was measured using a competitive protein binding assay (16). Normal values for 41 age-matched controls for the month of the study (Oct.) were 28.4 ± 9.8

Abbreviations: IF = index finger; GT = great toe; 25-OHD = 25-hydroxyvitamin D; BDI = Beck Depression Inventory.



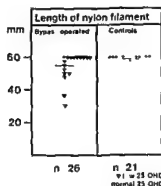


Fig 1 Absolute values of corneal sensitivity in 26 patients with jejunoileal bypass and in 21 controls. Mean values are indicated by solid lines

ng/ml. A single 24 hour urine sample was collected for measurement of calcium excretion.

The psychological test used was part of an expanded version of the Beck Depression Inventory (BDI) consisting of a 21 item questionnaire (2) and additional 14 items constructed to detect various autonomic nervous system manifestations. The items used to evaluate the autonomic nervous system were tremor, palpitations, constipation, dryness of the mouth, difficulty in urination and disturbed accommodation. The items used to demonstrate psychological symptoms related to asthenia were irritability, insomnia, fatigability and loss of libido (1). Intensity scores: 0=normal, 1=mild, 2=moderate, 3=severe.

#### Statistical analyses

Non parametric statistics were used. Comparisons were made using the  $\chi^2$  test and correlation coefficients by Spearman's rank correlation. Mean values were used to express the overall trend of results and one standard deviation (SD) to express the scatter.

## RESULTS

The corneal sensitivity and vibratory perception of each patient and control are shown in Figs 1 and 2.

Table I Number of patients with jejunoileal bypass and controls with reduced corneal sensitivity (threshold  $<55$  mm) and vibratory perception (IF threshold  $>5$  V, GT threshold  $>9$  V)

Threshold	Corneal sensitivity (mm)		Vibratory perception (V)			
	$<55$	$\geq 55$	$>5$ IF	$\leq 5$	$>9$ GT	$\leq 9$
Bypass-operated (n=26)	7	19	18	8	14	12
Controls (n=21)	1	20	3	18	3	18
$\chi^2$ test (p <)	0.05		0.005		0.01	

Table II Relationship of biological and psychological characteristics in 26 patients with jejunoileal bypass and the reduction of corneal sensitivity (threshold  $<55$  mm) and vibratory perception (IF threshold  $>5$  V, GT threshold  $>9$  V)

	Corneal sensitivity (mm)		Vibratory perc. (V)	
Threshold	<55	≥55	>5 IF	≤5
<b>Stools</b>				
≥3	6	7	17	1
<3	1	12	6	7
p	<0.05		<0.05	
<b>Paraesthesia</b>				
+	6	14	15	5
-	1	5	7	4
p	n.s.		<0.05	
<b>Muscle pains</b>				
+	4	1	6	0
-	2	18	17	8
p	<0.001		n.s.	

Fig 1 shows that some patients had low corneal sensitivity and that overall the considerable range of results in this group shows a similar wide scatter of results in the group for measurements of vibratory perception. There were significant differences between patients and controls with regard to corneal sensitivity ( $p < 0.05$ ) and to vibratory perception (IF,  $p < 0.05$ ; GT  $p < 0.01$ ) (Table I). The patients with low corneal sensitivity also had significantly

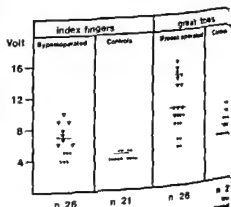


Fig 2 Absolute values of vibratory perception in 26 patients with jejunoileal bypass and in 21 controls. Mean values are indicated by solid lines

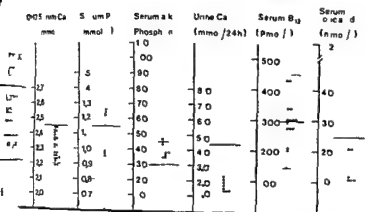


Fig. 3 Biochemical data from 26 patients with jejuno ileal bypass values  $\pm$  1 S.D. by solid and dotted lines.

perception ( $p < 0.05$ ). No correlations were observed between advanced age, reduced corneal sensitivity and vibratory perception.

Psychological results are shown in Fig. 3. The presence of undetectable or low 25-OH vitamin D below the normal range in 17 patients. The mean weight was  $39.1 \pm 11.0$  kg in these 17 patients ( $p < 0.001$ ) compared to the others ( $p < 0.001$ ). Serum 25-OH vitamin D was elevated in 10 patients, all had serum 25-OH vitamin D values below 10 ng/ml, serum calcium concentration and the urine calcium excretion were reduced.

25-OH vitamin D values were significantly reduced in the patients with reduced vibratory perception compared with the rest of the bypass group. Reduced corneal sensitivity was found among patients with low 25-OH vitamin D, whereas no correlation was found between low 25-OH vitamin D and reduced corneal sensitivity. Serum folate levels tended to be subnormal in the lower normal limit, whereas values were within the normal range in the other patients. No correlation between serum folate and

and B<sub>12</sub> values and the reduced corneal sensitivity or vibratory perception.

The average daily stool frequency of the patients was  $3.1 \pm 1.7$ . The number of daily stools was significantly related to both reduced corneal sensitivity and vibratory perception ( $p < 0.05$ ) (Table II). The presence of paraesthesiae also shows that the presence of paraesthesiae is related to reduced vibratory perception ( $p < 0.05$ ) but not to decreased corneal sensitivity.

Six patients with low serum 25-OH vitamin D complained of persistent muscle tenderness at rest. They had significantly reduced corneal sensitivity ( $p < 0.001$ ) and reduced vibratory perception of the lower extremities ( $p < 0.05$ ) compared to the rest of the patients.

Table III shows the number of patients with each score of the psychological tests related to autonomic nervous system. The correlation between the tests related to the autonomic nervous system and the reduced vibratory perception was not significant.

Table IV Scores of the BDI related to the autonomic nervous system and the relationship of these to corneal sensitivity (threshold  $< 55$  mm) and vibratory perception (IF threshold  $> 5$  V, GI threshold  $> 9$  V).

Threshold score	Corneal sensitivity (mm)		Vibratory perception (V)			
	$< 55$	$\geq 55$	$\leq 5$ IF	$> 5$	$\leq 9$ GI	$> 9$

0	3	5	3	5	5	3
$> 3$	3	6	0	9	1	

$\chi^2$  test ( $p$ ) n.s.  $< 0.05$

Distribution of the patients by intensity of BDI.

Score	Intensity of BDI		
	0	1	2

8	9	9
2	11	13

measured to the autonomic nervous system

perception was significant ( $p < 0.05$ ) (Table IV). No relationship was found between scores of items related to asthenia and to the reduction of sensory qualities.

## DISCUSSION

The present investigation revealed a reduced corneal sensitivity and vibratory perception in obese patients who had undergone intestinal bypass surgery. This suggests the presence of a neuropathy affecting both the peripheral sensory nervous system (vibratory perception) and the fifth cranial nerve (corneal sensitivity). These sensory abnormalities were related to disturbances in vitamin D metabolism which again were related to frequency of stools. Low 25 OHD values have previously been reported in patients operated upon with jejunioileal bypass (7, 8, 11, 13, 14, 20, 22). It is evident that the most severe sensory disturbances occurred in patients with low 25 OHD value, but the results do not lead to any conclusion as to whether vitamin D deficiency plays a role in the pathogenesis of the neuropathy or is merely an expression of severe multifactorial metabolic disturbance. Recently Halverson et al. (11) however suggested that vitamin D deficiency might induce neuromyopathy in patients who have undergone intestinal bypass surgery.

Muscle tenderness occurred in 6 patients, all with low 25 OHD values indicating myopathy, and we assume like other authors that vitamin D or its metabolites has an effect on striated muscle (3, 9, 13, 15).

The patients with abnormal vitamin D metabolism and reduced sensory qualities also had the highest frequency of stools and the largest weight losses. The desired weight reduction by jejunioileal bypass surgery was thus obtained at the expense of a severely disturbed vitamin D metabolism.

Factors other than disturbances in vitamin D metabolism are probably involved in the pathogenesis of reduced corneal sensitivity and vibratory perception. As shown in Table II, paraesthesiae were present in most of the patients and were related to reduced vibratory perception. These results indicate changes in the peripheral sensorimotor nervous system which could be due to lack of vitamin B<sub>12</sub>. The serum B<sub>12</sub> levels were normal, probably because the patients were receiving regular B<sub>12</sub> injections since the first postoperative

year (19). The folic acid levels were low, but do not correlate with the reduced sensory qualities. Another cause of the polyneuropathy could be a deficiency of thiamine (14), although we did not measure serum levels because none of the patients had any of the classical symptoms of thiamine deficiency. We did not find signs of diabetes either before or after surgery, which might have been responsible for the polyneuropathy. On the contrary, we noticed a decrease of fasting blood sugar compared with operative values, which is in accordance with the observations of Solhaug and Grundt (21).

Using the expanded BDI (2), no relationship was found between asthenia or the reduced sensory qualities, whereas items related to the peripheral nervous system showed a good correlation with reduced vibratory perception. This might indicate widespread changes in both the peripheral and central nervous system.

From a practical point of view, reduced corneal sensitivity may prevent the wearing of contact lenses. Reduced corneal sensitivity and vibratory perception as a part of polyneuropathy is a recognized problem which should be added to the increasing number of complications reported after jejunioileal bypass surgery.

## REFERENCES

1. Beck P & Hey H. Depression or asthenia? Metabolic disturbances in obese patients after intestinal bypass surgery. *Acta Psychiatr Scand* 54.
2. Beck A T, Ward C H, Mendelson M E & Erbaugh J K. An inventory for a depression. *Arch Gen Psychiatry* 4: 561, 1966.
3. Burge S J. Vitamin D, muscle and bone homeostasis. *Mineral Electrolyte Metab* 1: 5.
4. Bray G A, Greenway F L, Barry R E, J R, Fiser R L, Dahms W T, Atkinson Schwartz A A. Surgical treatment of obesity: review of our experience and an analysis of reports. *Int J Obesity* 1: 331, 1977.
5. Campbell J M, Hunt T K, Karam F, Forsham P H. Jejunioileal bypass as a treatment for morbid obesity. *Arch Intern Med* 137: 602, 1977.
6. Cochet P & Bonnet R. L'esthésiometrie: corrélation et intérêt pratique. *Bull Soc Ophtol* 54: 1961.
7. Compston J E & Creamer B. Plasma levels of intestinal absorption of 25 hydroxy vitamin D in patients with small bowel resection. *Gut* 19: 11.
8. Compston J E, Laker M F, Woodhouse J C, Horton L W L, Ayers A B, J & Pilkinton T R E. Bone disease after jejunioileal bypass for obesity. *Lancet* 2: 1, 1978.

- 10 B. Basen J F Francis M J O & L. Calcium uptake by sacroplasmic reticulum from vitamin D deficient animals. *Nature* 317:4
- 11 D. Backmann L & Espmark S. Surgical treatment of obesity. *Prog Surg* 14:46 1975
- 12 J. D. Wise L. Wazna M F & Ballinger. Jejunocolic bypass for morbid obesity. *Am J Surg* 131:1978
- 13 E. & Karner Jorgensen F. Quality of life in patients after bypass operation. *Ugeskr Læger* 137:1978
- 14 B. Lund B. Christensen M S. Lund B. & Sørensen O H. Impairment of vitamin D metabolism in patients with bypass operation for morbid obesity. *Scand (Suppl)* 674:73 1979
- 15 W. R. Himmreck, A S & Hardin C A. Effects of jejunoileal bypass for morbid obesity. *Arch Surg* 110:1079 1975
- 16 J. A. Russell R G G & Smith R. Clinical and therapeutic differences between vitamin D metabolites and analogues. *Clin Endocrinol Suppl* vol 7:191 1977
- 17 Lund B & Sørensen O H. Measurement of 25-hydroxyvitamin D in serum and its relation to intake and vitamin D intake in Danish population. *J Clin Lab Invest* 39:23 1979
- 18 M. M. Fickert. Fusion and laboratory percutaneous neurology. Thesis Aarhus 1967
- 19 N. N. Nelsen. Corneal sensitivity and hyperreflexia in diabetes mellitus. *Acta Ophthalmol* 1968
- 20 D. Roos. Neurological complications in patients with impaired B<sub>12</sub> absorption following partial gastrectomy. Thesis Copenhagen 1978
- 21 M. S. Schoen M S. Lindenbaum J A. R. & Holt P R. Significance of the 25-hydroxycholecalciferol in gastric. *Gastroenterology* 70:760 1976
- 22 J. H. Solhaug J H & Grund J. Metabolic effects of jejuno-ileal bypass for obesity. *Scand J Surg* 13:169 1978
- 23 S. L. Teitelbaum S L. Halverson J D. Bae L. & Haddad J G. Abnormal metabolism of vitamin D after jejuno ileal bypass. *Ann Intern Med* 86:789 1977

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

# Incidence of Urolithiasis Leading to Hospitalization in Finland

Markku Juuti and Olli P. Heimonen

*From the Department of Surgery, University Hospital of Kuopio  
and the Department of Community Health, University of Kuopio, Kuopio, Finland*

**OBJECT** The study population consists of 2304 patients discharged from all hospitals in all hospital districts in 1970. The incidence is 40 per 100 000 inhabitants per year, 74 for 127 for women. The age distribution resembles a Gaussian curve, with a peak between 45 and 54 for men and between 50 and 54 years for women. The male/female ratio was 2.7 in the entire population, about 1 in the age group 0-24 years, about 1.5 in the age group 25-74 years and about 1.5 in 75 years or older. The standardized incidence is highest in Southeastern Finland and in the Åland Islands and lowest in the coastal area of Western Finland. In the area with high incidence the age distribution of urolithiasis patients differs from that in the rest of the country. In the age groups over 40 the incidence of urolithiasis did not appear to decrease. This difference was attributed to some lifelong environmental exposure. The fixed incidence of urolithiasis leading to hospitalization was higher among urban than rural residents. Seasonal variation in the hospital admissions for urolithiasis was not evident. Temporal patterns of admissions were however dissimilar in urban and rural areas, and might reflect differences in the activities of urban and rural populations.

difference in the occurrence of urolithiasis between patients from rural and urban areas.

In an earlier study from the County of Uppsala in Sweden the incidence per 100 000 inhabitants per year was 74.5 (6) and later in Älvsborg County about 80 (1). There was no statistical difference between the rates among residents of cities and rural communities. A thorough study from Czechoslovakia revealed an average hospital admission rate of 101 per 100 000 inhabitants per year in 1950-1954 (11). The rate was very low among agricultural workers. A study from the USA showed an average hospital admission rate of 94.7 per 100 000 inhabitants per year with a range from 43.1 in Mississippi to 196.5 in South Carolina in 1952 (2).

The overall male/female ratio varies in different studies between 1.5 and 4.1 (9, 12-18). Season and climate have repeatedly been reported to influence the incidence of urolithiasis (5, 10, 13). In a study from Leeds, England (16) the rate of stone passage was about 50% higher in summer than in winter.

This study, based on the hospital discharge data of Finland, reports the incidence of urolithiasis according to age, sex, area of residence and season.

*Key words:* urolithiasis, urinary calculi, epidemiology.

*Acta Scand 206: 397, 1979.*

## MATERIAL AND METHODS

The study is based on the hospital discharge records registered by the National Board of Health from Jan. 1 to Dec. 31, 1970. The study population consists of all patients with urolithiasis and their controls with acute appendicitis and acute pancreatitis who were discharged from any hospital in the entire country during one year. Only the first discharge in that year has been taken into account in the analyses. Some comparisons were made between patients with urolithiasis and those with any other diagnosis.

Information about the resident population grouped according to age, sex and central hospital district on Dec. 31, 1970, was obtained from the Official Statistics of Finland (14). The population at the end of 1970 was 4 622

The incidence of urolithiasis has been reported in Finland from some other European countries (1, 7, 15, 17). An average of 30 per 100 000 inhabitants per year were admitted to hospital for urolithiasis in 1953 and 1954 (17). The reported number of patients treated for urolithiasis in Finnish hospitals increased more than 100-fold in the period 1950 years or so. The statistics revealed no

Table I Number of hospital admissions for urolithiasis in 1970 in Finland

Diagnosis	Men	Women	Total
Ureteral stone	1 643	549	2 192
Renal stone	216	187	403
Vesical stone	163	65	228
Nephrocalcinosis	54	133	187
Calculous pyelonephritis	21	31	52
Calculous pyonephrosis	5	6	11
Urolithiasis n o s	152	99	251
Total	2 254	1 170	3 324

habitants 2 233 658 men and 2 388 641 women. The country is divided into 21 central hospital districts; the population of which ranged from 20 789 in Åland to 995 854 in Helsinki.

The incidence rates were standardized by the direct method. When testing the seasonal variation, the method of Edwards was applied (3). In view of common practice and style, the term admission rate is employed here instead of discharge rate, although this introduces mild inaccuracy in the case of seasonal variation.

## RESULTS

There were 3 324 hospital admissions for urolithiasis in 1970 in Finland: 2 254 men and 1 170 women. Table I shows the distribution by different subgroups of the diagnosis. In further analyses pa-



Fig. 1 Standardized rates (per 100 000 inhabitants) hospital admissions for ureteral and renal stones in hospital districts in 1970 in Finland.

tients other than those who were admitted for ureteral or renal stone for the first time in 1970 were excluded, leaving 2 304 patients: 1 650 men and 654 women for study.

The age and sex distributions of the year's total admissions for ureteral and renal stones are shown in Table II.

Table II Hospital admission rates for ureteral and renal stones by age and sex in 1970 in Finland

Age (y)	Men		Women		Total	
	No. of cases	Rate (10 <sup>-5</sup> )	No. of cases	Rate (10 <sup>-5</sup> )	No. of cases	Rate (10 <sup>-5</sup> )
—4	0	0.0	0	0.0	0	0.0
5–9	1	0.5	1	0.5	2	0.5
10–14	2	1.0	3	1.5	5	1.3
15–19	18	8.3	22	10.6	40	9.4
20–24	79	34.2	61	27.8	140	31.1
25–29	127	74.5	54	33.2	181	54.4
30–34	149	101.9	57	39.9	206	71.3
35–39	193	138.4	68	50.1	261	94.8
40–44	229	155.8	56	37.8	285	96.6
45–49	240	183.5	68	45.7	308	110.1
50–54	155	145.2	69	52.1	224	93.6
55–59	179	162.7	63	45.7	242	97.6
60–64	135	133.5	56	42.1	191	81.6
65–69	92	126.8	38	36.0	130	73.0
70–74	37	79.7	20	25.3	57	43.3
75–79	14	55.0	18	37.1	32	43.3
80–	0	0.0	0	0.0	0	0.0
Total	1 650		654		2 304	49.8
Mean		73.9		27.4		

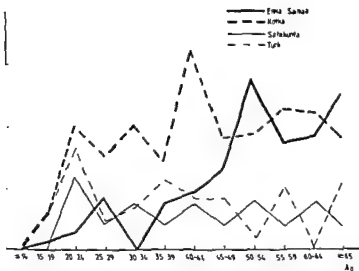


Fig 2 Hospital admission rates (per 100 000 inhabitants) for ureteral and renal stones by age in women from central hospital districts with a high rate (Etela Saimaa and Kotka) and a low rate (Satakunta and Turku) in 1970

Table II The peak age for men was 45-49 and for women 50-54 years. The male/female ratio was 2.7 and varied somewhat with age. 0-24 years about 1.25-74 years about 3.75 years and over 1.5.

Standardized incidence rates according to hospital district and sex are shown in Fig 1. Rates were highest in Southeast Finland and in the archipelago of Åland. The rates varied similarly in both sexes.

At the sex ratio, the incidence of ureteral and renal stones varied differently with age between districts with a high as opposed to a low rate.

For some densely populated central hospital districts, the age distributions of the incidence in high rate districts (Etela Saimaa and Kotka) and low rate districts (Satakunta and Turku) are shown in Fig 2 for women and in Fig 3 for men. Compared with the rest of the country, there was an apparently different pattern in Southeast Finland (Etela Saimaa and Kotka); here the incidence steadily increased with age, whereas in other parts of Finland the age distribution was Gaussian.

The frequency of admissions for ureteral and renal stones among residents of urban and rural communities is given in Table III. The residence area

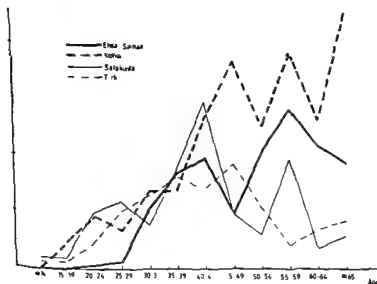


Fig 3 Hospital admission rates (per 100 000 inhabitants) for ureteral and renal stones by age in men from central hospital districts with a high rate (Etela Saimaa and Kotka) and a low rate (Satakunta and Turku) in 1970



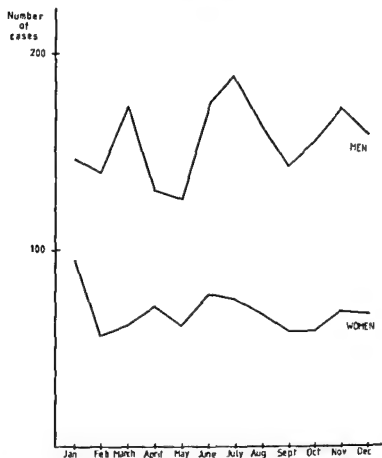


Fig. 4 Number of hospital admissions for urolithiasis by sex and month in 1970 in Finland

was available in 1 898 cases (82%). The annual incidence per 100 000 inhabitants was 52.0 in the urban areas and 30.2 in the rural areas. The sex ratio did not differ by the area of residence.

The monthly distribution of admissions for urolithiasis is shown in Table IV and Fig. 4. For comparison the table also gives the corresponding

admissions for acute appendicitis and acute pancreatitis. The number of admissions for urolithiasis was largest in July, and for acute pancreatitis in the summer months. The admissions for acute appendicitis fluctuated with no meaningful trend.

Table III Standardized rates of hospital admissions for ureteral and renal stones in urban and rural communities in 1970 in Finland

	No. of cases	Population	Rate (10 <sup>-5</sup> )
<i>Urban</i>			
Men	908	1 092 450	83.1
Women	308	1 247 858	24.7
Total	1 216	2 340 308	52.0
<i>Rural</i>			
Men	510	1 127 535	45.2
Women	172	1 130 493	15.2
Total	628	2 258 028	30.2

Table IV Number of hospital admissions for urolithiasis, acute appendicitis and acute pancreatitis by month in 1970 in Finland

	Urolithiasis			Acute appendicitis	Acute pancreatitis
	Men	Women	Total		
Jan	149	94	243	903	11 <sup>a</sup>
Feb	140	57	197	818	12 <sup>a</sup>
March	170	61	231	831	17 <sup>a</sup>
April	129	70	199	837	14 <sup>a</sup>
May	124	59	183	868	15 <sup>a</sup>
June	169	71	240	790	16 <sup>a</sup>
July	185	72	257	839	14 <sup>a</sup>
Aug	162	64	226	816	18 <sup>a</sup>
Sept	140	57	197	797	17 <sup>a</sup>
Oct	150	56	206	839	15 <sup>a</sup>
Nov	166	66	232	818	14 <sup>a</sup>
Dec	148	65	213	797	14 <sup>a</sup>

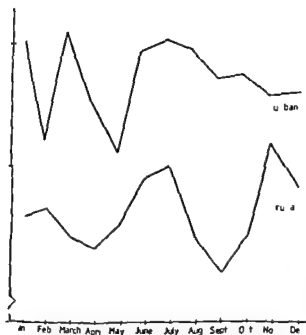


Fig. 5. Number of hospital admissions for urolithiasis by area of residence and month in 1970 in Finland.

admissions for ureteral stones (excluding with other types of urolithiasis) were also included with admissions for all other diseases. Admissions differed significantly for men ( $p < 0.001$ ) but not for women. No statistically significant variation of admissions by time tested by Edwards' method whether tested for in two- three or four month periods. It was the seasonal variation among males which was statistically significant when tested in three month periods.

The results are shown in Table V. The pattern of hospital admissions for urolithiasis differed between residents of urban and rural areas (Fig. 5).

## DISCUSSION

There is no ideal method for estimating the true rate of urolithiasis. An approach based on hospital admissions (discharges) clearly underestimates the true incidence but is useful for relevant reasons in a particular country if the network of hospitals is dense, if the organization of the hospital is uniform and unchanged, and if the data on admissions cover the entire country adequately. In the present study the possibilities for hospital admissions are considered to be essentially similar everywhere. All beds and personnel are fairly evenly distributed and medical practices carried out in a

rather uniform fashion. To avoid any effects of possible temporal changes in these factors, all patients hospitalized for urolithiasis in Finland during one year (1970) only were selected for the study. There is no reason to believe that this year was exceptional in any relevant way.

In the past 16 years the annual incidence of urolithiasis has increased from 3 to 5 per 10000 inhabitants. There is no reason to believe that the principles for admission for urolithiasis have changed strikingly during this period. However, hospital beds and admissions to general hospitals have both increased about twofold during this time (14). The proportional increase in the incidence is of the same order of magnitude as in a Swedish study (17) based on the frequencies of roentgenologically verified ureteral and renal stones. In that study the incidence rose in 15 years from 13 to 70 per 10000.

The age distribution of hospital admission rates

Table V. Number of hospital admissions for urolithiasis by sex and season in 1970 in Finland.

	Men	Women
Dec-Feb	351	139
March-May	336	106
June-Aug	403	137
Sept-Nov	369	101
$\chi^2$	4.84 NS	1.8 NS

for ureteral and renal stones in this study did not differ notably from those reported earlier in Scandinavia (1). It resembles the Gaussian distribution with a peak between 45 and 49 years for men and between 50 and 54 years for women.

The male/female ratio was 2.7 and varied considerably with age, amounting to about 1 in the 0-24 year group, to about 3 between 25 and 74 years and about 1.5 in the patients aged 75 or more.

Attempts to reveal possible local differences or seasonal variations in hospital admissions for urolithiasis have not been made earlier in Finland.

The standardized hospital admission rates showed marked differences between 21 central hospital districts. In addition, where the rates were highest (Etela-Saimaa, Kotka), the incidence of urolithiasis continued to increase with advancing age, without any marked decline among old people. This pattern was evident in both sexes. This finding supports the opinion that in these areas, prolonged exposure to some environmental factor(s) plays a role in the genesis of urolithiasis.

The area with the highest incidence matches the area of the Wiborg rapakivi massif. Also in the archipelago of Åland, where the incidence of urolithiasis was relatively high, rapakivi deposits are relatively common. Rapakivi granites contain, e.g., more fluoride-bearing minerals than do other rocks. This is clearly reflected in the ground water, the fluoride content of which is about 1.3-1.9 mg/l in the coastal region of Southeast Finland and about 0.06-0.13 mg/l in other parts of the country (8).

The hospital admission rate per 100 000 inhabitants per year was 52.0 in urban areas and 30.2 in rural areas. True rates were higher, since the residential community of the patient was not available in about 18%. It is, however, unlikely that this affected the urban/rural ratio, as experience has shown that this piece of information tends to be missing at random in the data. In Czechoslovakia there was a negligible number of cases of stone formers among farmers (11). This finding supports the view that the rising incidence of urolithiasis is associated with a high standard of living.

Three different approaches were utilized to examine the monthly and seasonal variations in the incidence of urolithiasis. Firstly, the numbers of hospital admissions for acute appendicitis and acute pancreatitis served as references. This comparison should reveal, at least partly, a possible systematic variation in hospitalization practices, particularly

for mild cases. The monthly admissions for urolithiasis varied differently from those for the other two diseases. Secondly, the number of total admissions for ureteral calculi was compared with the admissions for all other diseases. The monthly pattern for the former differed from the other admissions in men ( $p < 0.001$ ) but not in women. However, this rather wild fluctuation in admissions for ureteral calculi did not make it difficult to support the hypothesis that the reason for a seasonal variation in the occurrence of ureteral calculi is the seasonal contrast sharply in Finland. Thirdly, the analyses were performed assuming a constant rate of ureteral calculi over the year. According to this approach, the monthly differences were not statistically significant.

The monthly variation in the incidence of urolithiasis differed between urban and rural areas, both had a peak in July, but another peak in March in urban areas and in November in rural areas. This may partly reflect the physical activity of the population. In men there were three peaks in March, July and November. The peak in March is due to urban dwellers only, and that in November to the rural population only. This pattern was consistent also between districts, and is thus considered to be real. This finding should have been confirmed by other studies. Also the fact that physical activity plays some role in the incidence of urolithiasis calls for a specific study.

## ACKNOWLEDGEMENTS

This study was supported by the Academy of Finland, the Finnish Medical Society, Duodecim, and the Regional Fund of the Finnish Cultural Foundation.

## REFERENCES

1. Ahlgren S. A. & Lorstad M. Renal and ureteral calculi in a Swedish district. *Acta Chir Scand* 130: 344, 1965.
2. Boyce W. H., Garvey F. A. & Swanson J. Incidence of urinary calculi among patients in hospitals 1948-1957. *JAMA* 161: 141, 1956.
3. Edwards J. H. The recognition and cyclical trends. *Ann Hum Genet* 25: 81, 1961.
4. Estlander J. A. Frekvensen af calculi i Finland. *Finska Lak Sällsk Forh* 18: 106, 1911.
5. Frank M., de Vries A., Lazebnik J. & Kivimäki J. Epidemiological investigation of urolithiasis. *J Urol* 81: 497, 1959.

- Granberg I Renal and ureteral calculi: a study of occurrence in Sweden during 1911-1938 with 6 notes on the geographical distribution *Acta Scand* 101 17 1951
- Jonen A Über die Harnsteine Sonderabdruck *den Acta Soc Med Fenn Duodecim Ser B* 1 22 Fasc 3 1936
- Orimo P On the hydrogeology of the coastal region of southeastern Finland Geological Survey of Finland Bulletin 252 1971
- Rees J N, Neale F C & Posen S Urinary calculi: Clinical, biochemical and radiological studies in 100 patients *Med J Aust* 2 1049 1971
- Reid R H Quantitative composition of kidney stones *J Clin Chem* 7 546 1961
- Reid J External factors in the genesis of urolithiasis In *Renal stone research symposium* (ed Hodgkinson & B E C Nordin) pp 59-64 Churchill Livingstone London 1969
- Nordin B, Lindell B, Granberg P-O & Lindvall N Urolithiasis: A study of its frequency *Scand J Urol Nephrol* 10 150 1976
- Prince C L & Scardino P L A statistical analysis of ureteral calculi *J Urol* 83 561 1960
- Public Health and Medical Care 1969-1970 The Official Statistics of Finland XI 72 73
- Renvall G Über das Vorkommen von Harnsteinen in Finnland *Z Urol* 4 508 1910
- Robertson W G, Peacock M, Marshall R W, Speed R & Nordin B E C Seasonal variations in the composition of urine in relation to calcium stone formation *Clin Sci Mol Med* 49 597 1975
- Sallinen A Some aspects of urolithiasis in Finland *Acta Chir Scand* 118 479 1959/1960
- Transbol I & Frydendal N Endocrine and metabolic aspects of urology: Aetiology of stone formation in 145 renal stone patients *Acta Chir Scand (Suppl)* 433 137 1973

## ANNOUNCEMENTS

*The 21st Postgraduate Institute for Pathologists in Clinical Cytopathology* is to be given at The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital Baltimore Maryland USA April 14-25 1980. The full two-week program is designed for pathologists who are certified (or qualified) by the American Board of Pathology or their international equivalents.

The entire course is given in English and will provide an intense refresher in all aspects of the field of Clinical Cytopathology with time devoted to newer techniques special problems and recent applications. Application is to be made before March 7 1980.

For details write John K. Frost M.D. 610 Pathology Building The Johns Hopkins Hospital Baltimore Maryland 21205 USA.

*The Second International Symposium of Nephrology devoted to "Secondary Forms of Hypertension: current diagnosis and management"* will be held at Montecatini Terme (near Florence) Italy May 6-8 1980.

Information: Professor C. Bianchi, Centro Nefrologico, Clinica Medica Generale 2, University of Pisa, I-56100 Pisa, Italy.

*International Symposium on Infections in the Immunocompromised Host* will be held in Veldhoven (Eindhoven) The Netherlands June 1-5 1980.

Deadlines for registration March 1 1980; abstracts mailed by March 1 1980.

Further information: International Symposium on Infections in the Immunocompromised Host, Symposium Secretary, P.O. Box 252, 6710 BG Ede, The Netherlands.

*Second International Symposium on Computers in Critical Care and Pulmonary Medicine* will take place in Lund, Sweden, June 3-6 1980.

Correspondence regarding abstracts, papers, registration and accommodation: B. Richardson, Symposium Secretary, Department of Clinical Physiology, University Hospital, S-22185 Lund, Sweden.

*The II World Conference on Lung Cancer*, arranged by the International Association for the Study of Lung Cancer, will take place in Copenhagen and Malmö June 9-13 1980.

Further information: Congress Secretariat, Congress Service, Linde Allé 48, DK-2770 Copenhagen Ø, Denmark.

*The 5th International Conference on Synthetic Fibrinolytic Thrombolytic Agents—Progress in Fibrinolysis* will be held in Malmö, Sweden, June 17-20 1980.

The conference language is English and there will be scientific sessions including 4 poster sessions and simultaneous sessions. Conference topics will include: Plasminogen activator; Activation of fibrinolysis and abnormal fibrinolysis; Fibrinolysis and plasminogen chemistry; Inhibitors of fibrinolysis; Thrombolysis.

Deadline for abstracts: Feb. 29 1980.

For further particulars contact: Professor B. Nilsson, Secretary General, 5th International Conference on Synthetic Fibrinolytic Thrombolytic Agents, Coagulation Laboratory, Malmö General Hospital, S-205 21 Malmö, Sweden.

*The Seventh International Convocation on Immunology* will be held at Niagara Falls, New York, USA, June 1980. The theme of the program is "Immunology of Major Histocompatibility Complex".

Further information: Dr. James F. Mohn, The College of Immunology, Room 210, Sherman Hall, State University of New York at Buffalo, Buffalo, New York 14260.

*4th International Congress of Immunology of the International Union of Immunological Societies (IUIS)* will be held in Paris, France, July 21-22 1980.

Deadline for submission of abstracts: Jan. 14 1980.

Further information: Congrès Services Internationaux, Lefebvre, F-75009 Paris, France.

*8th International Congress of Physical Medicine and Rehabilitation: Disability—Prevention and Management* will be held in Stockholm, Sweden, Aug. 25-29 1980.

Time limits: submission of abstracts Jan. 1 1980; final registration May 1 1980.

Correspondence: Physical Medicine Congress, Convention Bureau, Jakobs Torg 3, S-111 65 Stockholm, Sweden.

# Systemic Capillary Leak Syndrome with Monoclonal IgG and Complement Alterations

*A Case Report on Systemic Capillary Leak Syndrome*

C G Lofdahl, L. Solvell, A. B. Laurell and B. R. Johansson

From the Department of Medicine, Mölndal Central Hospital, Mölndal, the Institute of Medical Microbiology, University of Lund, Lund, and the Department of Anatomy, University of Göteborg, Göteborg, Sweden

A case of the rare systemic capillary leak syndrome (SCLS) is described. The patient had attacks with muscle pain, weakness and sweating. He showed increased Hct values up to 62% and a decreasing plasma volume to about 40% during the attacks. The patient was in hypovolemic shock and BP was unmeasurable. Studies of labelled albumin during attack showed an increased transcapillary escape rate to about 20% compared to 6% when he was without symptoms. Monoclonal IgG with a constant concentration of about 5 g/l was found. Studies of the complement system during attack showed low C4 values and alterations among the C1 subcomponents and C1q-C1IA complexes suggesting a complement activation via the classic pathway. Hereditary angioedema was excluded by normal C1IA values. The complement activation might be part of the pathogenesis of the increased macromolecular permeability in this syndrome. A short review of cases reported earlier is given.

and capillary permeability. Components complement activation, transcapillary escape rate, albumin.

Acta Med Scand 206 405 1979

Syndrome with periodic systemic capillary leak (SCLS) resulting in hypovolemic shock has been described previously (1, 4, 9, 11, 12, 14, 15, 36). The disease seems to be very rare and only 8 cases have been reported in the literature. The present report describes one more patient with this syndrome. As noted in the patients described earlier, an association with a monoclonal gammopathy was found. The quantitative levels of complement factors indicated complement activation and consumption during attacks.

## CASE REPORT

In Dec 1975 a 44-year-old truck driver was admitted to Mölndal Central Hospital because of stiff painful muscles and epigastric pain. He had for many years had symptoms of gastritis but no peptic ulcer had been found on repeated X-ray examinations. Otherwise he had been healthy up to March the same year. From March to June 1975 he had had three episodes of tiredness, weakness and daphoresis. Each episode lasted 1-2 days but did not necessitate hospital care.

**Major attack.** In June 1975 he had had a more severe attack with the same symptoms and was admitted to another hospital. On admission the blood pressure was not measurable, the heart rate was 150 and Hct 79%. Macrodex® (500 ml dextran mean molecular weight 70000) and isotonic saline (2000 ml) were given. The symptoms subsided within 24 hours. Tests for adrenal insufficiency were negative. No definite diagnosis was established and the patient was discharged in good health.

**Minor attacks.** Characterized by tiredness, sweating, myalgia, weakness and a duration of less than 24 hours had been frequent (3-4 per week) during the autumn of 1975. The patient had noted that the attacks seemed to be elicited by heavy work.

On admission on Dec 1975 Hct was 62% and BP was not measurable. About 4000 ml isotonic saline were given and all symptoms disappeared within 24 hours.

Because of the history of attacks being precipitated by physical work, an exercise test on an ergometer bicycle was performed 8 days after admission (Fig. 1). At a work load of 100 W the patient felt dizzy and his systolic BP decreased to 60 mmHg (initial value 140/60). He was placed in a supine position and the BP normalized. Three hours later he became unconscious and had general convulsions for 1 min. Blood sugar was normal. Serum albumin decreased from 39 g/l before work to 32 g/l 4 hours after work (no fluid had been administered).

Neurological examination after the convulsions showed no abnormal findings. The BP was 100/60. His condition deteriorated again later during the same day. Systolic BP

Requests for reprints to C. G. Lofdahl, Lungkliniken, Renströmska sjukhuset, Fack S-407 60 Göteborg 17, Sweden.

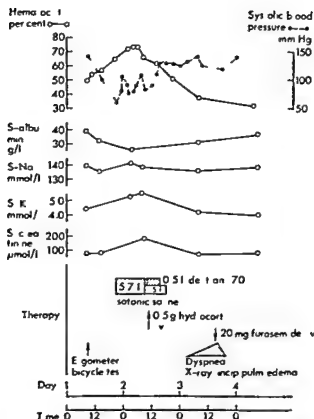


Fig 1 Laboratory parameters and clinical findings during a major attack probably elicited by an ergometer bicycle test.

decreased to 60 mmHg and Hct increased to 65%. Ringer solution (7200 ml i.v.) and fluid (3000 ml orally) were given during the following 12 hours. In spite of this Hct increased further up to 73%. There was no urine production during this time. Serum creatinine rose to 180 μmol/l, serum potassium to 5.5 mmol/l. Edema of the face and extremities developed. Macroderm® (500 ml) and hyaluronate (0.5 g) were given. BP rose to 120/70 with nifedipine and the diuresis was 100 ml/hour. An X-ray examination of the abdomen did not show any signs of ascites.

Two days after the exercise test the patient became dyspnoeic with basal pulmonary rales and an X-ray examination showed signs of incipient pulmonary edema. He was given 20 mg furosemide i.v. and the symptoms disappeared within a few hours.

A trial of prophylactic treatment with tranexamic acid (1 g t.i.d.) was started some days after the attack and the patient was discharged from hospital. There was, however, no evident effect of this treatment and minor attacks were noted two or three times weekly.

After 2 months of treatment with tranexamic acid (March 1976) the patient was readmitted in deep shock. He was cyanotic with unmeasurable BP. Cardiac arrest occurred and resuscitation with cardiac compressions was instituted. The patient soon regained consciousness. Isotonic saline and Macroderm® were given and his condition normalized within 3 days.

A further treatment with the prostaglandin synthase inhibitor domethac (25 mg t.i.d.) was then tried for 4 weeks, but any evident prophylactic effect. Two minor attacks occurred during this period.

The therapy was thereafter changed to prednisolone doses decreasing from 40 to 10 mg daily. Minor attacks occurred also on this treatment. In addition, the patient was given a  $\beta_2$ -adrenostimulating drug, terbutaline, increasing doses up to 30 mg daily (Fig. 1). The prednisolone was then successfully reduced and it was omitted. Five days after withdrawal of prednisolone in Nov. 1976 a study of the plasma volume and capillary escape rate of albumin was performed. The labelled albumin (see Methods and Results) was then omitted and 2 days later when the patient showed signs of a new attack the study was repeated. Eighty minutes after the injection of  $^{125}$ I-labelled albumin a constant infusion of terbutaline (5 μg/min) was started. Oral terbutaline was repeated 2 days later when the study was performed 4 days later when the patient was without symptoms.

During the following 74 months the patient was treated with prednisolone and terbutaline and had three attacks necessitating hospital care. All three started in connection with infections. The last attack occurred 70 months ago.

## METHODS

Clq, Clr, C3, C4, properdin and C1 esterase inhibitor (C1IA) were determined by electromicroimmunoassay described earlier (20, 37, 33). C1IA was also determined by an enzymatic test (17). Circulating complexes of complement components were shown by crossed immunoelectrophoresis (18). Quantitative determinations of complement components were performed (21). IgG, IgA and IgM were measured by immunoelectrophoresis (18).

Albumin turnover studies were performed with  $^{125}$ I-labelled albumin (27). The transcapillary escape rate of albumin was determined by following the plasma volume for 1.5–2 hours. The plasma volumes were then extrapolated to the active zero time. The extravascular volumes were calculated from the plasma volume and the estimated whole body Hct (venous Hct  $\times 0.9$ ).

Table 1 Blood volume measurements during and after an attack

	Nov 3 1976 (Before)	Nov 5 1976 (During)
Plasma volume (ml/kg b.wt.)	39.4	20.3
Erythrocyte volume (ml/kg b.wt.)	24.9	23.0
Blood volume (ml/kg b.wt.)	64.3	43.3
Venous Hct (%)	43	49

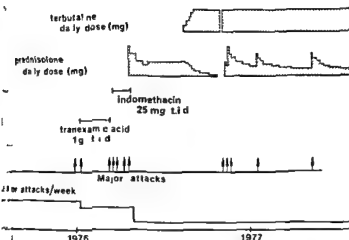


Fig 2 Prophylactic drug therapy during 2 years

## RESULTS

### Physical findings

During the attacks the patient consistently had a haematocrit value up to a maximum of 79% in spite of considerable amounts of parenteral fluid. After attacks the Hct values became subnormal (the observed value 27%) and normalized during following days.

Leukocyte counts were increased during attacks. The maximum value noted was  $59 \times 10^9/l$ . Abnormal values were observed within 2 days after an attack. The differential count during one attack showed 91% segmented neutrophils, 0.5% banded neutrophils, 8% lymphocytes and 0.5% monocytes. Thrombocytes were normal.

Marrow examined in a symptom free period was normal.

### Findings

The patient showed tachycardia and non specific ST and T changes during attacks.

### Chemical findings

Serum creatinine values were normal between attacks. During several attacks the patient was anuric and serum creatinine rose to a maximum of  $4 \text{ mol/l}$ . A moderate increase in serum potassium was also found. A Pitressin® test between two attacks showed a normal concentration ability. No proteinuria was found during the attacks.

### Proteins

Albumin was decreased at the onset of the attacks. As expected the lowest values (19 g/l)

were observed after fluid administration. On two occasions the serum albumin was measured during attacks before any therapy had been given. A decrease from about 40 to about 30 g/l was recorded (Fig 1).

Albumin kinetics and plasma volumes were studied with  $^{125}\text{I}$  labelled albumin three times: twice between attacks and once during an attack (Fig 3, Table I).

The first investigation when the patient was without symptoms showed normal conditions. The plasma volume was 39 ml/kg b wt and the calculated erythrocyte volume 25 ml/kg b wt. The albumin transcapillary escape rate was 6%/hour. Two days later when the patient had an attack a significantly decreased initial plasma volume was found (20 ml/kg b wt) and the erythrocyte volume was 23 ml/kg b wt. Hct was initially 59% and in

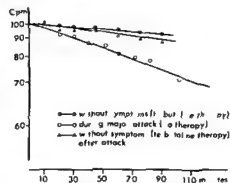


Fig 3 Disappearance of  $^{125}\text{I}$  labelled albumin from the intravascular compartment. The transcapillary escape rate is 19%/h during attack and normal (6–8%) during other studies.



Table II Complement components other serum proteins and Hct values during different therapy regimens

	Reference values	March 15 1976 (Serious major attack after fluid administration)	March 17 1976 (Two days after attack)	April 1 <sup>st</sup> 1976 (Moderate attack before fluid administration)	April 4 <sup>th</sup> 1976 (Moderate attack after fluid administration)
Clq (%)	76-136	-	87	100	125
Clr (%)	71-133	-	-	123	115
Cls (%)	72-146	-	187	138	>200
C3 (%)	70-136	38	106	110	111
C4 (%)	53-207	9	74	35	37
CIIA (%)	72-153	48	140	99	110
	20-30*	15	-	21	25
Properdin (%)	57-153	-	-	87	94
Clr-Cl <sub>s</sub> -CIIA complexes (%)	45	-	-	-	-
	11-25	12	-	48	45
Clr-Cl <sub>s</sub> complexes	Not quantitative	-	-	No	105
S-albumin (g/l)	36-54	24	41	-	31
S-IgG (g/l)	6.5-15	3.3	7.8	13.0	16
S-IgA (g/l)	0.8-2.4	0.6	1.0	1.5	1.5
S-IgM (g/l)	0.3-2.0	0.7	1.2	2.1	1.6
Hct (%)	36-48	59	33	54	60

\* Immunochemical method • Enzymatic method

creased during the study to 70%. This indicates a further loss of about 600 ml of the plasma volume. At the end of this investigation the plasma volume was 14 ml/kg b wt (assuming a constant erythrocyte volume during this period). The albumin transcapillary escape rate was markedly increased to 19%/hour. No significant change occurred when terbutaline was given 80 min after the <sup>125</sup>I albumin injection at a constant rate (5 µg/min) for 40 min. 7 days later when the patient was free from symptoms the study was repeated. The plasma volume was restituted (37 ml/kg b wt). A slight increase in the calculated erythrocyte volume was found from 23 to 20 ml/kg b wt. The transcapillary escape rate of albumin was 8%/hour.

**Serum immunoglobulins** (Table II) IgG was normal between attacks and during attacks when no therapy was given. It was low (3.3 g/l) when plasma substitutes and isotonic saline had been administered. IgA followed the same pattern. IgM was increased (2.1-2.6 g/l) during attacks before fluid had been given. Otherwise it was normal.

Serum electrophoresis showed a monoclonal component in the anodal gamma region. Immunoelectrophoretic analysis showed an IgG $\lambda$ . The concentration was rather constant 4-5 g/l both during attacks and in attack free periods.

No abnormal proteins were found in the supernatant after concentration by polyethylene glycol or by Amicon® filtration.

**Complement system** (Table II) Low C4 (35 and 37%) were found during two moderate attacks. In an attack free period C4 was 88 (92%). The C3 values on these occasions were within the normal range. During the moderate attacks a disproportion was found between the concentrations of the Cl subcomponents with levels of Clr and Cls compared to Clq. Furthermore the precipitation line appearing on agarose gel of Cls was diffusely outlined indicating a change in composition of the Cls precipitate complex. This appearance in normal serum and in serum when the patient was symptom free.

Analysis of serum by crossed immunoelectrophoresis showed increased amounts of Cls-CIIA complexes during attacks. The levels of IgG were within normal limits on these occasions.

After fluid administration in connection with a serious major attack a pronounced decrease was found in albumin, IgG, C3, C4 and CIIA. The value of IgG was however more expected from the reduced plasma volume. Four days later the same parameters analyzed.

Oct 12 1977  
(No symptoms  
on steroid and  
terbutaline  
therapy)

74

175

123

73

158

28

40

-

87

12

13

-

normalized Cl inactivator levels determined biochemically and enzymatically were within per normal range during the moderate attacks did not differ from the value in a sample obtained in an attack free period. Properdin was normal in the samples obtained during moderate attacks.

**Urine.** During and between attacks vanillylmandelic acid, norepinephrine and epinephrine in urine were all normal. Studies of histamine, histamine, and 5-hydroxytryptamine during attacks did not show any increased histamine liberation.

## DISCUSSION

Patients with SCLS characterized by a marked decrease in plasma volume and hypovolemic shock have to our knowledge been described in the literature (1, 4, 9, 11, 12, 14, 15, 36). In a recently published review (1) Atkinson et al. included one case described by Preston et al. (29) but the possibility of that patient probably had another condition. Five additional cases (7, 22, 30, 34) of a similar syndrome occurring in relation to major trauma and delivery have been reported. In 2 patients died in the acute attack and it is difficult to evaluate whether the trauma per se might have

contributed to the symptoms. Therefore they are omitted in the present discussion.

The 9 patients including the present one with no relation to trauma are presented in Table III. Six were men and all were white. The debut of the syndrome occurred in middle life. There was no evidence of heredity. The symptoms occurred intermittently and the duration of the attacks was 2-14 days. The interval between attacks varied from 4 days to 12 months. In 6 of the reported cases infection seemed to be a precipitating factor. In 2 women the attack occurred premenstrually. Our patient had several attacks related to strenuous physical activity.

The prognosis seems to be very poor. Five of 9 cases have died during an attack after intermittent symptoms for 3-8 years. Two patients were alive after 3-6 years observation. In 2 patients the outcome is unknown.

During a typical attack our patient—like cases described earlier—exhibited stiff, painful muscles and some facial and neck edema, indicating that the musculature and to some extent the subcutaneous tissue compartments were subjected to extravasation of plasma during attacks. No renal leakage of protein could be demonstrated. Neither were there any obvious signs indicating that the pulmonary microcirculation was affected during attacks. The patient rather had episodes of incipient pulmonary edema in the recovery phase after attacks, presumably because of hypervolemia. We therefore conclude that the major cause of the increased albumin transcapillary escape rate and the concomitant plasma volume reduction was a temporary increase of the macromolecular permeability in the capillary beds of skeletal muscles and connective tissues (3, 23). Accordingly we have performed an electron microscopic study of the microvessels in muscle biopsies obtained both in a free interval and during an attack. These findings will be reported separately (13).

The plasma volumes during attacks have varied between 42 and 74% of normal in different patients (Table III). The transcapillary escape rate of albumin during an attack was 19%/hour in our patient and 32%/hour in one of the patients described earlier (4). Such high transcapillary escape rates seem to be unique for SCLS and are even higher than those seen in severe burns (4). Slight but constant elevations of transcapillary escape rate of albumin have been found in many other

- 5 DeBracco M M & Manni J A Serum levels of C1q C1r and C1s in normal and pathological sera *Arthritis Rheum* 17 121 1974
- 6 Edwards O M & Bayliss R I S Idiopathic oedema of women *Q J Med* 177 125 1976
- 7 Fishbein M C State D Hirose F & Castagna J Capillary leak syndrome with massive intestinal edema after appendectomy *Am J Surg* 127 740 1974
- 8 Garrot P O Crossed immunoelectrophoresis *Scand J Clin Lab Invest (Suppl)* 124 39 1972
- 9 George C Regnier B Le Gall J R Gastinne H Carlet J & Rapin M Hypovolemic shock with oedema due to increased capillary permeability *Intens Care Med* 4 159 1978
- 10 Hint H The pharmacology of dextran and the physiological background for the clinical use of Rheomacrodex and Macrodex *Acta Anesthesiol Belg* 2 119 1968
- 11 Horwath M Hagstrom J W C Riggins R C K & Luckey E H Hypovolemic shock and edema due to increased capillary permeability *JAMA* 200 111 1967
- 12 Jacob R F Waterhouse C & Tobin R Periodic disease associated with muscle destruction *Am J Med* 55 105 1973
- 13 Johansson B R & Lofdahl C G Ultrastructure of the microvessels in skeletal muscle in a case of systemic capillary leak syndrome *Acta Med Scand* 206 413 1979
- 14 Larcen A Calmai M Heully M C & Helmer J Choc cyclique par exagération de la perméabilité capillaire *Presse Med* 77 1931 1969
- 15 Larcen A Laprevote M C & Lambert H Cyclical shock with hyperglobulinemia *Bibl Anat* 13 343 1975
- 16 Laurell A B Johansson U Mårtensson U & Sjöholm A G Formation of complexes composed of C1r C1s and C1 inactivator in human serum on activation of C1 *Acta Pathol Microbiol Scand C* 86 299 1978
- 17 Laurell A B Lindegren J Malmros I & Mårtensson H Enzymatic and immunochemical estimation of C1 esterase inhibitor in sera from patients with hereditary angioneurotic edema *Scand J Clin Lab Invest* 24 221 1969
- 18 Laurell A B Mårtensson U & Sjöholm A G C1 subcomponent complexes in normal and pathological sera studied by crossed immunoelectrophoresis *Acta Pathol Microbiol Scand C* 84 455 1976
- 19 — Studies of C1 subcomponents in chronic urticaria and angioedema *Int Arch Allergy Appl Immunol* 54 434 1977
- 20 — The development of simple tests for C1q C1r C1s C2 and properdin In *Clinical aspects of the complement system* (ed W Opferkuch K Rother and D R Schultz) pp 12–14 Thieme Verlag Stuttgart 1978
- 21 — Quantitation of C1r C1s-C1 inactivator complex by electroimmuno assay *Acta Pathol Microbiol Scand* In press 1979
- 22 Luke I W & Rubinstein E Fatal post-operative shock due to massive angioneurotic edema *Obstet Gynecol* 83 372 1967
- 23 Majno G Ultrastructure of vascular membrane *Handbook of physiology section 7 Circulation* (ed W F Hamilton and P Dow) pp 25–31 Williams and Wilkins Baltimore 1965
- 24 Marder R J Rent R Choi E Y & Gross C1q deficiency associated with urticarial lesions and cutaneous vasculitis *Am J Med* 61 461 1977
- 25 Neri Serneri G G Gensini G F & Altarelli R Increased capillary permeability in leukaemia and asplenic anaemia *Acta Haematol* 52 376 1974
- 26 Parving H H Microvascular permeability in untreated and treated essential hypertension and during acute induced hypertension *BMJ* 13 335 1975
- 27 Parving H H & Gynzelberg F Escape rate of albumin and plasma volume in essential hypertension *Circ Res* 32 643 1973
- 28 Parving H H & Rossing N Simultaneous determination of the transcapillary escape rate of albumin in normal and long term juvenile subjects *Scand J Clin Lab Invest* 32 239 1973
- 29 Preston G M Russell Rees J & Spahn G L man with cyclical edema *Guy's Hosp Rep J* 40 1970
- 30 Robin E D Carey L C Gremik A & Gaudin R Capillary leak in primary edema *Arch Intern Med* 130:66 1972
- 31 Sissons J G P Peters D H Gwyn W B Boulton Jones J M & Goldsmith H J Sissons angio-oedema and hypocomplementemia *Lancet* 2 1350 1974
- 32 Sjöholm A G Complement components in human serum and plasma quantitated by electroimmunoassay *Scand J Immunol* 4 25 1975
- 33 Sjöholm A G Mårtensson U & Laurell A B C1r levels in normal human sera determined by electroimmunoassay *Acta Pathol Microbiol Scand C* 84 425 1976
- 34 Smullens S N & Templeton J J Hypovolemic shock due to massive edema cardiopulmonary bypass *J Thorac Cardiovasc* 61 348 1972
- 35 Svensjö E Persson C G A & Arfors K E Effects of bradykinin and terbutalin on microvascular leakage and its relation to microvascular resistance *Microvasc Res* 11 425 1976
- 36 Weinbren I Spontaneous periodic edema *Acta Med Scand* 254 1963

# Ultrastructure of the Microvessels in Skeletal Muscle in a Case of Systemic Capillary Leak Syndrome

Bengt R. Johansson and Claes Goran Löfdahl

From the Department of Anatomy, University of Göteborg, Göteborg, and the Department of Medicine, Mölndal Central Hospital, Mölndal, Sweden

**ABSTRACT** The microvessels of skeletal muscle examined electron microscopically in a case of systemic capillary leak syndrome (SCLS). One biopsy taken in a free interval of the disease and one 6 hours after the onset of an attack with hypovolemia. The microvascular endothelium exhibited a large number of multivesicular bodies, especially in the specimen obtained during an attack. This indicates a high heterophagic activity of the endothelium. A blebbing of the luminal surface of the vascular endothelium was observed in the attack specimen. Since a complement activation seemed to occur during attacks, the blebbing is tentatively indicated as a sign of a complement mediated injury of the endothelium, leading to a breakdown of the cellular barrier. This mechanism might explain the dramatic increase of microvascular permeability and plasma proteins during an attack of SCLS. The study did not indicate that the increase might depend on some disturbance of the transendothelial barrier transport function, nor could any openings in the endothelial junctions, as in inflammation be demonstrated. Regionally the periendothelial basal lamina appeared thickened, a finding which seems to be common in angiopathies of different kinds.

**Keywords:** capillary permeability, complement activation, electron microscopy, endothelium.  
*Acta Med Scand* 206: 413, 1979.

In a previous paper (7) we described the clinical picture in a case of the rare systemic capillary leak syndrome (SCLS). The patient exhibited severe attacks of hypovolemia and shock, which were elicited by physical activity or infections. As in other reported cases of SCLS, serum analysis revealed a monoclonal IgG gammopathy (see Löfdahl et al. (7) for references) and we also found evidence of a complement activation during attacks. Extravasation of plasma probably occurred to a considerable extent in the skeletal muscles, which were stiff and

tender during attacks. The present study accounts for electron microscopic examinations of muscle biopsies from this patient.

## MATERIALS AND METHODS

Small muscle biopsies were obtained surgically from the biceps brachii muscle, once during a free interval of the disease (non attack specimen) and once in a hypovolemic state, about 6 hours after onset of symptoms, before treatment was instituted (attack specimen). Control biopsies were obtained from the deltoid muscle of a 28 year old man without any history of cardiovascular disease. The whole biopsies were immersed over night in a mixture of 1% paraformaldehyde and 1.25% glutaraldehyde in 0.05 M Na cacodylate buffer, pH 7.2. Small blocks of tissue from the superficial parts were postfixated in 1% OsO<sub>4</sub> in 0.1 M Na cacodylate buffer, pH 7.2, dehydrated in ethanol and embedded in Epon according to routine procedures. Sections were cut with a diamond knife on an LKB Ultratome and examined in a Philips EM 300 electron microscope after staining with lead citrate and uranyl acetate.

## RESULTS

The ultrastructural appearance of the muscle cells and of the connective tissue compartments within the musculature of the patient appeared normal and did not differ from the control specimens. Thus, no degenerative changes in the muscle cells or inflammatory processes in the tissue were observed. The frequency of microvessels was not quantified but there were no signs of destruction or breakdown of the endothelial lining, as has been reported in scleroderma and systemic lupus erythematosus (9).

Since the patient exhibited episodic increases of macromolecular permeability (7) the ultrastructural substrates for transendothelial permeation of macromolecules, namely the plasmalemmal vesicles of the endothelial cells (12) and the tight junctions of the endothelium (6)

findings of Friedman and Laufer (2) who observed in the electron microscope blebbing of beating rat heart cells in culture after treatment with specific antibodies and complement. In their experiments the blebbing led to a total ballooning and eventual disruption of the cells. Considering the signs of a complement activation in the patient during attacks (7) the endothelial blebbing described here might represent the beginning of a complement mediated cytotoxic process leading to irreversible damage to the affected cells and thereby to an increased protein permeability. The idea of an endothelial cell destruction as an important initial step in the SCLS seems to be supported by the duration of the attacks 1-4 days in our patient and 2-14 days in other cases reported (7). Such a time course could indicate that the attack does not subside until the endothelium has regenerated for example by mitoses (1). Unfortunately it was not possible to perform repeated biopsies on our patient during attacks in order to follow the development of the submicroscopic changes.

In the epithelium of rat vas deferens Friend and Farquhar (3) found evidence that multivesicular bodies played the role of digestive vacuoles in the degradation of proteins that had been transported into the cells. The high number of multivesicular bodies observed in the biopsy specimens from our patient may possibly represent a high heterophagic activity in the endothelium. The data also indicate the possibility of a more extensive formation of multivesicular bodies during an attack than during a silent phase of the disease.

## REFERENCES

Dvorak A M, Mihm M C Jr & Dvorak H F. Morphology of delayed type hypersensitivity reactions in man. II. Ultrastructural alterations affecting

- the microvasculature and the tissue mast cells. *Invest* 34: 179, 1976.
- 2 Friedman I & Laufer A. Electron microscopic studies of the effect of an 'heart attack' on complement on beating rat heart cells in culture. *J Cell Cardiol* 8: 41, 1976.
- 3 Friend D S & Farquhar M G. Function of autophagosomes during protein absorption in the rat vas deferens. *J Cell Biol* 35: 357, 1967.
- 4 Gonzalez Angulo A, Fraga A & Mraz G. Microscopic alterations in capillaries of skeletal muscles in polymyositis. *Am J Med* 45: 873, 1968.
- 5 Jerusalem F, Rakusa M, Engel A G & Donald R D. Morphometric analysis of muscle capillary ultrastructure in muscular myopathies. *J Neurol Sci* 23: 391, 1974.
- 6 Karnovsky M J. The ultrastructural basis of capillary permeability studied with peroxidase histochemistry. *J Cell Biol* 35: 213, 1967.
- 7 Lofdahl C G, Solvell L, Larzell A, Johansson B R. Systemic capillary leak with monoclonal IgG and complement activation: case report on an episodic syndrome. *Acta Scand* 706: 405, 1979.
- 8 Majno G & Palade G E. Studies on effects of histamine and serotonin on capillary permeability. An electron microscopic study. *Biophys Biochem Cytol* 11: 571, 1961.
- 9 Norton W L, Hurd E R, Lewis D C & Ziff M. Evidence of microvascular injury in scleroderma system (lupus erythematosus). Quantitative study of the microvascular bed. *J Lab Clin Med* 71: 59, 1968.
- 10 Scheppokat K, D. Hammersen F, Bracks W. Idiopathische Ödeme, Angiopathie und erweiterte Körperhöhlenräume. *Wochenschr* 55: 1137, 1977.
- 11 Shafrq S A, Mithorath A T & Gorn L M. Electron-microscope study of muscle and vascular changes in polymyositis. *J Cell Biol* 94: 139, 1967.
- 12 Simonescu N, Simonescu M & Puck T. Permeability of muscle capillaries to erythrocyte hemoglobin. *J Cell Biol* 57: 474, 1973.
- 13 Zeligs J D & Wollman S H. Endothelial blebbing and phagocytosis of blebbed epithelial cells in vitro. *J Cell Biol* 1977.

# Miliary Tuberculosis

Brita Stenius Aarniala and Pentti Tukiainen

*From the Department of Pulmonary Diseases, University Central Hospital, Helsinki, Finland*

**ACT** Twenty six cases of miliary tuberculosis were studied in retrospect. The mean age of the patients was 62 years. Eighteen patients had been treated with corticosteroids or cytotoxic drugs. A limited manifestation of tuberculosis had previously been verified or suspected in ten cases. Fever was present in 85% of the patients, frequently associated with fatigue or abdominal pain. Serum alkaline phosphatase was elevated in 81% of the patients. Minor haematological abnormalities (anaemia, leukopenia or pancytopenia, stimulation of lymphocytes or chronic myeloid leukaemia) were found in 16 cases and pancytopenia, stimulation of lymphocytes or chronic myeloid leukaemia in 13 patients. Other findings were pleural effusion, mediastinal node enlargement, opacities suggesting pneumonia or old, possibly tuberculous lesions. Antituberculous therapy was initiated in 12 patients, two of whom died within a few days. There was a high frequency of liver or system involvements. Laparoscopy or liver needle biopsy and other diagnostic procedures in patients with suspected miliary tuberculosis should be undertaken in suspected cases.

**Key words:** miliary tuberculosis, respiratory distress syndrome.

Acta Med Scand 206 417 1979

In the last three decades several authors have drawn attention to miliary or disseminated tuberculosis as posing diagnostic problems (1-9, 11). In a review (8) described 129 fatal cases in which the principal cause of death was tuberculosis. In about 30% of the cases tuberculosis was not diagnosed until autopsy and it appeared that miliary or disseminated tuberculosis constituted the majority of these undiagnosed cases. The concept of miliary tuberculosis was introduced by Root et al (11) to designate cases of disseminated tuberculosis in which the typical clinical

and radiographic features were absent. It seemed that a changing pattern (7, 6) was becoming discernible in miliary tuberculosis: the disease often presenting as an obscure illness in the elderly.

Having recently encountered some diagnostically very difficult cases of disseminated tuberculosis we decided to study the diagnostic aspect of all relevant cases seen at Helsinki University Central Hospital and Aurora Hospital during the past 7 year period.

## MATERIAL AND METHODS

The material was collected with the help of the computer data on final diagnosis, coded according to international practice. In addition 5000 final autopsy records were examined. The hospital records of all 25 cases traced in this way were available for retrospective study. The 26th patient, a man with miliary tuberculosis and respiratory distress syndrome, was referred for treatment and included in the material at a time when the present report was already under preparation.

The material comprises 16 females and 10 males with a mean age of 62 years (range 41-80). The chest X rays were re-analyzed by the authors.

## RESULTS

On admission the majority (85%) of the patients complained of fever (Table I). A body temperature of 39°C or higher was measured in 63% of the patients during the hospital stay. Fatigue, loss of weight and abdominal pain were each complaints of about one third of the patients. Eight patients complained of dyspnoea. One of these cases calls for more detailed comments.

## CASE REPORT

A man aged 50, in whom cirrhosis of the liver had been diagnosed earlier, presented with fever and severe dyspnoea. Rales being noted basally on both lung fields. His arterial  $PO_2$  was 57 mmHg on inhalation of 35%  $O_2$ .

Table I *Presenting symptoms in 26 cases of miliary tuberculosis*

	No. of cases
Fever (38°C)	23
Loss of weight	10
Abdominal pain	9
Fatigue	9
Dyspnoea	8
Nausea and vomiting	6
Cough	4
Headache	3

through a Ventri mask. The chest radiograph showed enlarged upper mediastinum, faint hazy opacities basally on both sides and a small parenchymal infiltration in the right lower lobe. The diaphragm was bilaterally elevated. Clinically the patient suffered from the respiratory distress syndrome. Neither the dyspnoea nor the hypoxia responded to treatment with digitalis, diuretics, broad spectrum antibiotics or corticosteroids. After a few days of antituberculosis treatment the dyspnoea disappeared and the auscultation finding was normal. Within 3 weeks the arterial O<sub>2</sub> tension rose to 73 mmHg when the patient was breathing air. The diagnosis of tuberculosis was eventually confirmed when the patient's condition allowed mediastinoscopy and a tuberculous glandular abscess was found.

ESR was elevated (mean 64.8 mm/h, range 14–150) in 23 out of 26 cases; in 6 cases it was 100 mm/h or higher. Alkaline phosphatase was elevated in 17 (81%) out of the 21 patients who underwent the test (mean 919 U/l, range 318–2231). It should be pointed out that liver cirrhosis could account for the elevated value in 3 cases. Serum transaminase was normal in most cases. The tuberculin test was performed in only 10 cases, 1–2 TU being positive in 3 and 10 TU in another 3 cases.

The frequency of haematological abnormalities (Table II) in this series has to be evaluated in the light of the fact that for various reasons many patients were inadequately examined. The following haematological investigations had been performed: tests for Hb in 26 patients, total WBC in 23, differential count in 21 and thrombocyte count in 20. Bone marrow aspirate was examined in 11 patients and showed no specific abnormalities. An unspecific plasma cell reaction was found in 2 patients, one of whom also presented with pancytopenia. In the other case of pancytopenia in our material the haematological diagnosis had been made and steroid treatment started 10 years prior to the

Table II *Haematological findings in 26 cases of miliary tuberculosis*

	No. of cases
No haematological changes	1
Slight changes	
Anaemia	14
Shift to the left	10
Thrombocytopenia/thrombocytosis	9
Leucocytosis	6
Severe changes*	
Lymphoid cells in bone marrow	3
Pancytopenia	2
Chronic myeloid leukaemia	1

\* Only Hb was determined in two cases, 1% WBC in one case.

\* Several of these findings were occasional, in one and the same patient.

onset of miliary tuberculosis. In 2 cases lymphoid cells were found but no specific diagnosis was made. In both of these cases the diagnosis was CML in combination with miliary tuberculosis.

Miliary mottling was seen in the chest graphs of 11 patients (37%) (Table III). In these cases the chest radiograph was normal at admission; the mottling changes appeared at a later stage. In 2 cases the primary findings were pleural effusion and diffuse parenchymal infiltrates, miliary mottling appearing at a later time. In 2 cases an enlarged mediastinum occurred in combination with miliary

Table III *Chest radiographic findings in 26 cases of miliary tuberculosis*

Abnormal findings*	No. of cases
Miliary mottling or nodular shadowing	11
Pleural effusion	4
Enlarged mediastinal glands	2
Parenchymal infiltrate interpreted as pneumonia	4
Inactive pulmonary tuberculosis	7
Fibrosis (scleroderma)	1
Atelectasis (carcinoma of upper mediastinum)	1
Normal	1

\* Several findings sometimes presented in the same radiograph.

# Source of final diagnosis and ground for starting treatment in 26 cases of miliary tuberculosis

Final diagnosis	No. of cases			
	Total	Treatment started exclusively before specific diagnosis was established	Treatment started after specific diagnosis	Not treated
Logical verification	2	1	1	
Macroscopic findings	4	2	2	
Abdominal	3	1	2	
Microscopic and/or X-ray findings alone	16	2		14
	26	7	5	14

18 (58%) of the 26 cases were fatal (Table V). In 10 cases death was attributed to malignant disease and the miliary tuberculosis was taken to be secondary. In 14 cases (54%) tuberculosis was diagnosed unexpectedly at the post mortem examination. In 7 cases treatment had been started before diagnosis and in 5 cases after the exact diagnosis had been made (Table V). The treatment was given in almost all the treated cases. In two cases tuberculosis was not suspected until miliary

mottling became apparent after several weeks of severe disease. Both these patients died shortly after antituberculosis treatment had been instituted.

Three of 11 patients with symptoms for less than two months died against 7 of 15 with symptoms for a longer period.

In the autopsied cases tuberculosis was found in different organs in various combinations. Typical tuberculous changes were found in the spleen, the liver or the peritoneal glands in all cases. In addition

## Source of diagnosis and course of disease in 12 treated cases of disseminated tuberculosis

Miliary mottling on chest X-ray	Diagnostic measures resulting in pathological diagnosis	Results of tests for M. tuberculosis	Response to treatment
Present	Cutting needle lung biopsy (TruCut)	Acid fast smear from lung specimen positive; sputum culture positive	Good; died 3 years later from perforation of the colon
Absent	Laparoscopy; spleen biopsy	Smear and culture from spleen specimen positive	Good
Absent	Laparoscopy; biopsy from peritoneum and lymph node	Culture from gastric lavage fluid positive	Good
Absent	Needle liver biopsy	Negative (sputum, urine, liver specimen)	Good
Absent	Laparoscopy; spleen biopsy	Negative (sputum, urine)	Good; died of bleeding venous ulcer 3 months later
Present	Cutting needle lung biopsy (TruCut)	Negative (sputum)	Good
Absent	Mediastinoscopy; biopsy from hilar lymph node	Negative (sputum)	Good
Present		Culture positive from spinal fluid and gastric lavage	Good
Present		Sputum culture negative	Good
Absent		Sputum culture positive	Good
Present	Autopsy	Sputum culture positive; result not known until post mortem	Died 4 days after treatment
Present	Autopsy		Died 4 days after treatment



Table VI Chronic diseases diagnosed prior to onset of the symptoms of miliary tuberculosis in 26 cases

	Survivors (N)	Non survivors (N)
Previously healthy	5*	3*
Chronic disease		
Emphysema and TB pleurisy previously		1*
Diabetes and non specific arthritis	1	
Rheumatoid arthritis		2*
Scleroderma and myeloid leucaemia		1*
Pancytopenia		1*
Hodgkin's disease		1*
Carcinoma		1*
Cirrhosis of the liver	2	1*
Chronic pyelonephritis and resection of the stomach earlier	1	
Chronic glomerulonephritis and uraemia		2
Pemphigoid erythema multiforme	1*	
Diabetes and recurrent cerebrovascular thrombosis		1
Schizophrenia		1
Total	10	16

\* Includes one patient lacking IgM and IgA and with low IgG values and one who possibly had previously suffered from tuberculous coxitis

\* Treated with corticosteroids

Includes two patients with a possible history of tuberculosis disease (upper lobe calcification, fistulating lymphadenitis)

\* Treated with antitumour chemotherapy

ion involvement of the lung parenchyma, hilar nodes or pleura was found in all cases except one. Other organs showing tuberculous changes were the kidneys (4 cases), the suprarenal glands, the heart, the bone marrow (2 cases each), the brain, the meninges and the lumbar spine (spondylitis) (1 case each).

In the surviving patients the important diagnostic procedures were needle biopsy of the lung (Tru Cut), mediastinoscopy, laparoscopy, laparotomy or needle biopsy of the liver. In some of these cases therapy had been started before the diagnosis had been confirmed.

Sputum specimens for bacteriologic examination had been taken from 17 cases. Three of these yielded positive cultures for TB bacilli, while all direct smears for acid fast bacilli in sputum were negative.

Tuberculosis had been found or suspected in a total of 10 patients. The diagnosis of pulmonary or glandular tuberculosis was confirmed in 3 patients. A spontaneously healed tuberculosis was plausible in 7 patients, in whom either lesions in the upper lobe were found or a history of pleurisy, spondylitis, coxitis or febrile lymphadenitis was present. One patient had a history of familial tuberculosis in 11 cases, 9 of them fatal.

In several cases a pre-existing disease contributed to the diagnostic difficulties (Table VI). Three of the 16 patients who died of tuberculosis had previously been healthy, whereas this was the case in 6 out of 10 diagnosed, treated and surviving patients. Six patients had previously been treated with corticosteroids and three with cytotoxic drugs.

## DISCUSSION

All the patients included in this study were considered to be cases of miliary tuberculosis either by the clinician or, in the fatal instances, by the pathologist on the basis of the necropsy report. Sufficient evidence of disseminated spread of tuberculosis was, in our opinion, present in all cases.

Miliary tuberculosis is known to present frequently as pyrexia of unknown origin. Intermittent fever is often only moderate (1, 10, 11). Common to the patients described in other reports, most of our material ran a temperature of over 39°C in the early stage of the disease. Loss of weight, loss of appetite, abdominal pain and dyspnoea are often reported in connection with miliary tuberculosis (10) and are supported by our findings. However, many of the symptoms and signs in our material could be attributed to some other co-existing disease.

Respiratory distress syndrome in connection with miliary tuberculosis has been described by several authors. Most of the cases have been fatal (14). de Silva et al. (15) described a patient who developed the symptoms and signs of respiratory distress within 9 days of anti-tuberculous chemotherapy. The patient with respiratory distress in our material is the only miliary tuberculosis in our material in which the syndrome and surviving case described in the literature.

Elevation of alkaline phosphatase in connection with miliary tuberculosis is thought to be a sign of infiltrative disease of the bone (16). It was found by Munt (9) in about 50% of the cases reported on. In our material elevation of alkaline phosphatase was found in 10 patients.

case was found in 81% of the cases compared with the results of Gneco and Chmel (3) who found a percentage of 86.

Tuberculin test was performed in less than 50% of our patients. All the tested cases belonged to groups which were not covered by the BCG vaccination scheme instituted in Finland in 1941. It can be assumed that the positive tuberculin test is not a result of vaccination. The results of the previous tuberculin tests were not available for comparison. In the cases with negative tuberculin test repeated testing at a later stage might have given positive results as indicated by Glasser et al.

Opinions differ concerning the interpretation of the haematological abnormalities encountered in cases of disseminated tuberculosis. Anaemia, leucopenia, eosinophilia and monocytosis have been found to occur as a result of antituberculosis treatment and can thus be directly associated with tuberculosis (2). Patients with leukaemic blood picture or pancytopenia in the series of Glasser et al. did not survive. In many cases it may be difficult to interpret whether the haematological abnormalities are secondary to tuberculosis or whether they constituted a predisposing factor.

Shift to the left was the commonest haematological feature found in our material. The leucopenia in one of our two patients had been present several years earlier. The other patient recovered with antituberculosis drugs which resulted in recovery and disappearance of the blood abnormalities.

Retardation of erythrocyte sedimentation by mottling is the classical finding in the chest x-ray in miliary tuberculosis. The absence of mottling is likely to add to the diagnostic difficulties. In 8 out of our 14 cases diagnosed at autopsy the chest radiograph had not suggested miliary tuberculosis. However, when re-evaluated retrospectively four of these 8 chest radiographs showed miliary mottling. Enlarged mediastinal lymphatic nodes have occasionally been associated with miliary tuberculosis and were present in 4 of our cases. This agrees with the results of Reed et al. who found enlarged mediastinal glands in three adult patients.

Autopsy as a means of detecting chorionitis was undertaken in only one case in our material, the result being negative. The bone marrow was frequently examined but the aspirated material was not fixed in paraffin as suggested by

Schleicher (14) to facilitate the diagnosis of a possible tuberculosis from the marrow specimen.

Most of our surviving patients were previously healthy or suffered from a chronic disease not giving symptoms indicative of disseminated tuberculosis. However, in many of the cases with a fatal course of miliary tuberculosis the symptoms of fever, weight loss, haematological changes and abdominal pain were attributable to pre-existing disease. In one of our cases anaemia and some months later myeloid leukaemia were diagnosed during antituberculosis treatment for lung tuberculosis. The antituberculosis drugs were at first thought to be the cause of the blood disorders and they were therefore withdrawn after 4 months of treatment. Attention was thereafter focused on the haematologic disease and after a few weeks of steroid therapy the patient died of miliary tuberculosis. This case resembles one presented by Munt (9) in which steroid treatment possibly enhanced the fatal miliary spread of tuberculosis from a previously diagnosed and treated lesion. The appearance of a new severe disorder in a patient with tuberculosis may require transfer to another hospital where several diagnostic and therapeutic problems have to be solved. It is understandable that the antituberculosis treatment may not be paid enough attention in such circumstances.

In the fatal cases in our material the possibility of tuberculosis had—mostly because of other co-existing disease—been taken under sufficient consideration. Many of the patients would eventually have succumbed to their severe chronic disease but life might have been prolonged by some months or even some years had the tuberculosis been treated. Our findings give reason to emphasize the importance of starting antituberculosis treatment in time: almost all the treated cases recovered. The results of the applied diagnostic tests and the autopsy findings indicate that laparoscopy may be a useful procedure in patients with fever and elevated alkaline phosphatase of unknown origin. In patients with diffuse pulmonary shadowing needle biopsy of the lung may be valuable. If the patient's condition does not allow these procedures or if the results are negative a therapeutic test with antituberculous drugs should always be undertaken. Miliary tuberculosis seems to be a condition which is chiefly found among elderly patients and which in the presence of other severe chronic diseases frequently escapes clinical detection.

Table VI Chronic diseases diagnosed prior to onset of the symptoms of miliary tuberculosis in 26 cases

	Survivors (N)	Non survivors (N)
Previously healthy	5*	3
Chronic disease		
Emphysema and TB pleurisy previously		1 <sup>b</sup>
Diabetes and non specific arthritis	1	
Rheumatoid arthritis		2 <sup>b</sup>
Scleroderma and myeloid leucaemia		1 <sup>b</sup>
Pancytopenia		1 <sup>d</sup>
Hodgkin's disease		1 <sup>b</sup>
Carcinoma		1 <sup>d</sup>
Cirrhosis of the liver	2	1 <sup>d</sup>
Chronic pyelonephritis and resection of the stomach earlier	1	
Chronic glomerulonephritis and uraemia		2
Pemphigoid erythema multiforme	1 <sup>b</sup>	
Diabetes and recurrent cerebrovascular thrombosis		1
Schizophrenia		1
Total	10	16

\* Includes one patient lacking IgM and IgA and with low IgG values and one who possibly had previously suffered from tuberculous coxitis

<sup>b</sup> Treated with corticosteroids

<sup>c</sup> Includes two patients with a possible history of tuberculosis disease (upper lobe calcification fistulating lymphadenitis)

<sup>d</sup> Treated with antitumour chemotherapy

tion involvement of the lung parenchyma hilar glands or pleura was found in all cases except one. Other organs showing tuberculous changes were the kidneys (4 cases) the suprarenal glands the heart the bone marrow (2 cases each) the brain the meninges and the lumbar spine (spondylitis) (1 case each).

In the surviving patients the important diagnostic procedures were needle biopsy of the lung (Tru Cut) mediastinoscopy laparoscopy laparotomy or needle biopsy of the liver. In some of these cases therapy had been started before the diagnosis had been confirmed.

Sputum specimens for bacteriologic examination had been taken from 17 cases. Three of these yielded positive cultures for TB bacilli while all direct smears for acid fast bacilli in sputum were negative.

Tuberculosis had been found or suspected in a total of 10 patients. The diagnosis of pulmonary or glandular tuberculosis was confirmed in 3 patients. A spontaneously healed tuberculosis was plausible in 7 patients in whom calcified lesions in the upper lobe were found or in whom lesions of pleurisy spondylitis coxitis or fistulating lymphadenitis was present. One patient with a history of familial tuberculosis in 11 cases of whom 3 had died of the disease.

In several cases a pre-existing disease may have contributed to the diagnostic difficulties. Three of the 16 patients who died of the disease had previously been healthy whereas in the other case in 6 out of 10 diagnosed treated and in 10 patients. Six patients had previously been treated with corticosteroids and three with cytostatics.

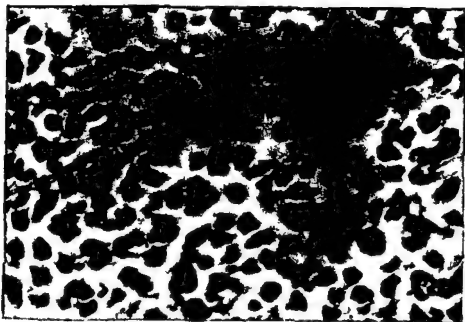
## DISCUSSION

All the patients included in this study were considered to be cases of miliary tuberculosis. The diagnosis was made by the clinician or in the fatal instances by the pathologist on the basis of the necropsy. There was sufficient evidence of disseminated spread of tuberculosis in our opinion present in all cases.

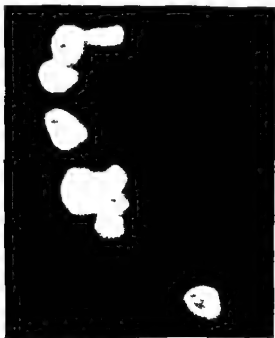
Miliary tuberculosis is known to produce frequently as pyrexia of unknown origin. The fever is often only moderate (1, 10, 11). Core temperature in our material ran a temperature of over 37°C in the stage of the disease. Loss of weight, loss of appetite, abdominal pain and dyspnoea are often reported in connection with miliary tuberculosis (10, 11). These symptoms and signs in our material could have been attributed to some other co-existing disease.

Respiratory distress syndrome in connection with miliary tuberculosis has been described by several authors. Most of the cases have been fatal. de Silva et al. (15) described a patient who died of the symptoms and signs of respiratory distress appearing within 9 days of antituberculous treatment. The patient with respiratory distress in miliary tuberculosis in our material is the first case and surviving case described in the literature.

Elevation of alkaline phosphatase in connection with miliary tuberculosis has been reported. It may be a sign of infiltrative disease of the liver. It was found by Munt (9) in about 20% of the cases reported on. In our material elevation of alkaline phosphatase was found in 10 patients.

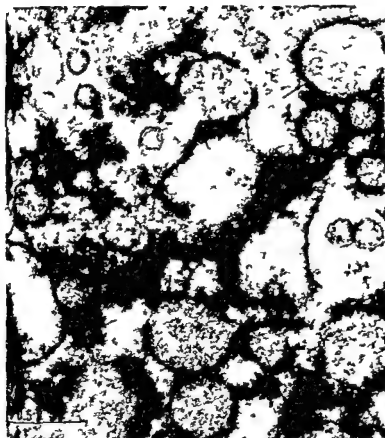


*Fig 2* Tumour cells from infiltrate in spinal vertebra. Highly pyronophilic elements indicating the presence of RNA and active protein synthesis (methylgreen pyronin, initial magnification  $\times 240$ )



*Fig 3* Immunofluorescent tumour cells with massive contents of IgG (kappa). Virtually all elements stained positively with FITC-conjugated anti IgG and anti kappa chains





*Fig 3* High power resolution electron micrograph demonstrating ribosomes (arrows) attached to the outside of the membranes surrounding vacuoles with amorphous material

ly large infiltrates of a brownish red soft tumour which extends with destruction of notably the lower t and the upper lumbar vertebrae causing extrinsic compression of the spinal cord at the level of L<sub>5</sub>. Foci of tumour tissue were also present within the ribs mainly on the right side in the left iliac bone and in the base of the skull corresponding to the right fossa.

The kidneys were enlarged the right weighing 230 g and the left 85 g. They had smooth surfaces but the hilar areas were swollen and rather pale. The other organs were acutely congested and no extra-osseous infiltrates were found.

Main fixed material mounted in paraffin blocks was stained and stained routinely with haematoxylin and eosin-saffron in addition to histochemical staining with methylgreen-pyronin. An immunoperoxidase stain for immunoglobulins was also performed (Pathology Department of Pathology Norwegian Radium Hospital Oslo).

Sections of tumour tissue from the spine, pelvic bones and skull showed largely dense infiltrates of plasma cells but also some bi- or multi-nucleated giant cells. Most tumour elements did definitely not have the appearance of typical plasma cells (Fig 1). On the other hand virtually every tumour cell proved to be markedly immunophilic (Fig 2).

The renal glomeruli appeared normal but numerous large hyaline and intensely pyroninophilic tubular casts were demonstrable by light microscopy. The affected tubules were distended and many revealed calcifications within necrotic epithelial cells. Multinucleated giant cells were often observed near atrophied and/or calcified epithelial elements and the surrounding interstitial tissue showed a slight chronic inflammatory reaction. The spleen, lymph nodes and liver were devoid of any conspicuous changes. In particular there were no infiltrates of plasmacytoid cells or any evidence of lymphoma.

#### *Electron microscopy*

Formalin fixed tumour tissue from bone marrow (spine, ribs, skull) obtained at autopsy was postfixed in 1% osmium tetroxide in Tyrode's solution at pH 7.4 for one hour. Dehydration was carried out in graded ethanol and the samples were embedded in Epon 812, sectioned on a LKB ultramicrotome, stained with lead citrate and uranyl acetate and examined in a Jeol 100B Electron Microscope I.

The tumour cells from the base of the skull, the ribs and the spinal column all showed principally the same ultrastructural features. The autolytic changes were however pronounced and made the morphological evaluation difficult. The cells did not reveal lymphocytic features as the cytoplasm was abundant and with a

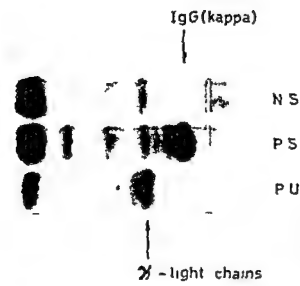


Fig. 4 Agarose gel electrophoresis of the patient's serum (PS) and urine (PU) demonstrating a monoclonal paraprotein in the serum and Bence Jones protein in the urine. Significant amounts of albumin were also present in the latter. NS = normal serum.

cytoplasmic ratio of approximately 1:3. The nuclei showed signs of autolysis, with a patchy chromatin distribution. A nucleolus was often present.

The cytoplasm contained numerous round vacuoles, often filled with an amorphous material. The vacuoles were surrounded by a lamellar membrane on the outer side of which ribosome-like structures were irregularly attached (Fig. 1). Typical flat cisternae of endoplasmic reticulum were almost totally absent. The Golgi apparatus was either completely lacking or only remnants could be seen.

The mitochondria were swollen with loss of matrix cristae, as seen in autolytic tissues.

### Immunological Investigations

#### Studies on serum

Serum protein electrophoresis was performed in 1% agarose gel (8). Immunoelectrophoresis was carried out on glass plates in agarose gel with antibodies against IgG, IgA and IgM, as well as against kappa and lambda light chains. Serum immunoglobulins were quantitated by the single radial immunodiffusion technique of Mancini et al. (9).

Agarose gel electrophoresis (Fig. 4) demonstrated a distinct M-component in the late beta<sub>2</sub>-position, making up 25 g/l serum. The other immunoglobulins in the gamma region appeared to be suppressed as evaluated by inspection of the electropherogram. Immunodiffusion verified this impression, as IgA made up 2 g/l and IgM 0.4 g/l serum (lower normal range). Immunoelectrophoresis showed that the M-component belonged to the IgG(kappa) class and the results of this investigation were otherwise comparable with the immunodiffusion data.

#### Studies on urine

After concentration of fresh morning samples on ultrafilters (concentrated  $\times 300$ ) agarose gel electrophoresis and immunoelectrophoresis were carried out with the same techniques as for the serum samples. Light chains of kappa type were demonstrable by immunoelectrophoresis and the light chains were located in the position of the electropherogram (Fig. 4). In addition to the Bence Jones protein.

#### Immunofluorescence studies

Bone marrow specimens obtained post mortem were transferred to EDTA-coated tubes, converted to smudge preparations being made with approximately 300,000 cells on each slide. The cells were stained with FITC-conjugated anti-immunoglobulin antibodies: anti-F(ab), anti-IgG, anti-IgA, anti-IgM, anti-IgE, as well as with kappa and lambda light chain types (5). The procedure of the ensuing microscopy adopted from Forre (4).

Large cellular infiltrates from the spinal cord and skull stained with anti-F(ab), and 100% of the infiltrative cells stained with IgG (Fig. 5) as well as with kappa light chains. No cellular elements were positive for the other antisera tested. Immunofluorescence confirmed the results of the immunoelectrophoresis.

### DISCUSSION

The present case demonstrates several features. The patient had hypercalcaemia, renal function and extensive skeletal metastases similar to those present in classical myeloma. Histologically, however, the tumour cells were initially classified by different pathologists as resembling those of an amelanotic melanoma, a seminoma or a malignant lymphoma. There were many small plasmacytoid elements and a few large giant cells, but typical plasma cells were not found. A large amount of IgG(kappa) paraprotein was present in serum and the urine contained significant amounts of kappa type Bence Jones protein.

The patient was only 24 years old, which is unusual in a case with the present clinical and immunological picture. The cellular pattern seen at light microscopy is partly compatible with that seen in Waldenström's disease, but this possibility can be excluded because macroglobulinemia was not present. Waldenström (13) has stated that he has seen a patient with multiple myeloma below the age of 30 years and only a single one in the third decade. Howell and Aletanian (14) have

and three cases of myelomatosis in patients of aged 22 years of age and Wille et al (14) have only encountered a 32 year-old patient with chain disease

Gross autopsy findings were typical of classical myelomatosis with extensive central skeletal involvement no extra-osseous infiltrates and systemic myeloma kidneys histologically as is histochemically The other internal organs including liver spleen and lymph nodes were all unremarkable The tumour elements however were definitely not typical plasma cells either by morphology or by electron microscopy Histological examination revealed massive infiltration by mainly mononuclear cells of varying size and with relative scant cytoplasm Most nuclei were more or less centrally located and there were several scattered and multi nucleated giant cells All tumour elements were histochemically strongly pyro-nuclear indicating the presence of RNA and active protein synthesis

For morphological studies alone was available for the ultrastructural studies with the ensuing limitations of autolysis The vacuoles containing the electron dense material most probably represent dilated cisternae of endoplasmic reticulum the finding of the attached ribosomes supporting this view The shape and the size of the endoplasmic reticulum may also be affected by the accumulation of material distending the cisternae The almost total absence of Golgi structures may reflect abnormalities of structure and function but the influence of this must be considered Altogether the ultrastructural findings indicate that the tumour elements are abnormal plasmacytoid cells with accumulated immunoglobulins

Immunofluorescence and peroxidase studies indicated that the tumour cells were producing immunoglobulin and demonstrated that virtually all tumour elements contained gamma heavy chains and kappa light chains thus producing the IgG class of immunoglobulin found in serum

We have thus reported a malignant immunoblastic tumour with tumour cells differing from conventional plasma cells but producing large amounts of immunoglobulin These elements cannot represent those of lymphatic leukaemia because such cells seldom contain intracellular immunoglobulin and the clinical picture as well as the histological pattern were incompatible with leukaemic disease Immu-

noglobulin containing macrophages have been reported however but these contained lambda as well as kappa light chains

A certain amount of evidence indicates on the other hand that immunoglobulins can be formed by large pyroninophilic lymphocytes These large cells which probably made up the great bulk of the tumour masses in our patient are compatible with young plasma cells or plasmacytes

An immunoblastic sarcoma would seem to be a morphologically reasonable differential diagnosis but this condition is primarily a lymph node disease and thus not compatible with the present findings Typical Reed Sternberg cells were not observed and the findings in the current case are otherwise also not in concert with malignant lymphogranulomatosis The reticulum cell sarcoma of bone originally described by Parker and Jackson (11) would provide a structurally satisfactory explanation of the mononuclear cells seen in the tumour tissue of our patient To our knowledge these cells do not usually produce immunoglobulin at least not to the same extent as observed in the current case

The patient had used hashish and amphetamine regularly during the last 7-8 years previously also LSD on a few occasions The use of hashish is known to cause inflammatory disorders of notably the respiratory tract (12) but there are no available reports of a possible tumourigenic effect of this drug A case of acute leukaemia is known to have occurred in an LSD addict but a possible causal relationship remains to be established (6) Newell et al (10) found that the use of amphetamine was associated with an increased risk of Hodgkin's disease but no significant association was found between the use of amphetamine and development of this or other types of malignant lymphoma in a large series reported by the Boston Collaborative Drug Surveillance Program (3) A possible relationship between addiction to narcotic drugs and development of B-cell derived malignancies cannot however be definitely excluded at the present time

In conclusion the tumour in our patient appears to represent a previously unrecognized immunoblastoma intermediate between multiple myeloma and a tumour originating from immature plasma cells The syndrome is compatible with and supports the theory that different forms of malignant lymphoproliferative disorders correspond to different stages in the development of the B lymphocyte to the mature plasma cell



## REFERENCES

- 1 Axelsson U, Bachmann R & Hallen J Frequency of pathological proteins (M-components) in 6995 sera from an adult population. *Acta Med Scand* 179: 235, 1966
- 2 Berkel J, Granillo-Bodansky C & Borne A E G K. V. D. Acute renal failure associated with malignant lymphoproliferative disorder with monoclonal light chain immunoglobulin production. *Scand J Haematol* 20: 377, 1978
- 3 Boston Collaborative Drug Surveillance Program. Amphetamines and malignant lymphoma. *JAMA* 229: 1462, 1974
- 4 Forre Ö. Studies on the antigen-combining variable region of human immunoglobulins. Thesis. Universitetsforlaget, Oslo, 1977
- 5 Forre Ö, Natvig J B, Froland S S & Johnson P M. Distribution of heavy chain variable region ( $V_H$ ) subgroups on human lymphocytes. *Scand J Immunol* 5: 1221, 1976
- 6 Grossbard L, Rosen D, McGilvray E, de Capoa A, Miller O & Bank A. Acute leukemia with Ph<sup>1</sup> like chromosome in an LSD user. *JAMA* 205: 791, 1968
- 7 Hewell G M & Alexanian R. Multiple myeloma in young persons. *Ann Intern Med* 84: 441, 1976
- 8 Johansson B G. Agarose gel electrophoresis. *J Clin Lab Invest (Suppl)* 174: 7, 1972
- 9 Mancini G, Carbonara A O & Heremans J F. Immunochemical quantitation of antigens by radial immunodiffusion. *Immunochemistry* 1: 235, 1965
- 10 Newell G R, Rawlings W, Kinnear B K, Henderson B E, Daorsky R, Moss Thompson R & Sheehan W W. Case-control study of Hodgkin's disease. I. Results of the international questionnaire. *J Natl Cancer Inst* 51: 1437, 1973
- 11 Parker F Jr & Jackson H Jr. Primary reticulum cell sarcoma of the bone. *Surg Gynecol Obstet* 1939
- 12 Tennant F S, Preble M, Prendergast I, Ventry P. Medical manifestations associated with hashish. *JAMA* 216: 1965, 1971
- 13 Waldenström J. Diagnosis and treatment of multiple myeloma. Grune & Stratton, New York and London, 1970
- 14 Wille L E, Förre Ö, Mödén E & Österlund L. Light chain disease—en forkäpsform av plasmacellomatos. *Tidsskr Nor Lægeforen* 93: 686, 1971

# Rheumatoid Arthritis, Immune Complex Disease, and Hypereosinophilic Syndrome

## Report on a Case

G H Ilerdal B Marjanovic and H Åberg

From the Department of Internal Medicine University Hospital Uppsala Sweden

**TRACT** A patient with typical rheumatoid arthritis is presented. After a short period of the disease hypereosinophilic syndrome (HES) developed. Asculitis, pulmonary fibrosis and thrombosis of the disease took a malignant course. The patient died within a year after the diagnosis of HES. High levels of rheumatoid factor were manifested and total complement (CH<sub>50</sub>) was very low and eating an active disease. As HES has been suggested to have an autoimmune aetiology these findings are interesting. Positive rheumatoid serology has very rarely been reported in patients with this syndrome.

**Key words:** hypereosinophilic syndrome, immune complex disease, rheumatoid arthritis, rheumatoid factor.

Acta Med Scand 206 429-1979

Hypereosinophilic syndrome (HES) is an uncommon entity and has, according to the literature, a variable manifestation. The aetiology is a matter of controversy. Some authors have claimed it to be an autoimmune disease (9, 18, 20), a hyperreactivity state (14) or of neoplastic origin (1). However, it seems clear that the syndrome can be very serious and that the patient may run a downward course with a fatal outcome within a few years, regardless of treatment (6). We report a patient with rheumatoid arthritis in whom HES developed, leading to death within a year.

## CASE REPORT

A 47-year-old woman had been hyposensitized against pollen in the 1940s because of allergic rhinitis with good result. In 1959 she had had a cutaneous eruption during administration of penicillin. In 1968 she devel-

oped myocarditis of unknown aetiology with subsequent complete recovery both clinically and electrocardiographically.

**Present illness.** In Sept. 1975 the patient presented at her local hospital with fever, pain, morning stiffness and slight swelling of the wrists, elbows, knees and ankles. She had lost weight and complained of tiredness. ESR was 30 mm/h. She had slight leucocytosis with 8% eosinophils but otherwise the laboratory tests showed nothing abnormal. She was treated as a case of rheumatoid arthritis, first with analgesics and later, as the symptoms deteriorated, with cortisone. In the spring of 1976 the latex test for rheumatoid factor (RF) became positive. There was a constant leucocytosis of about  $18.0 \times 10^9/l$  and an eosinophilia of 15%. The ESR had now increased to 90 mm/h.

In June 1976 a morbilliform cutaneous eruption with itching occurred and the eosinophils had increased to 18%. As a drug reaction was suspected, all drugs except cortisone were withdrawn. In spite of this the patient had episodes of fever up to 39°C, new cutaneous eruptions, Quincke's oedema and painful joints. This state continued all the summer and general muscle weakness also gradually developed with a puffy feeling under the feet.

In Dec. 1976 the patient was referred to our hospital because of a thrombosis of the right lower leg, verified by phlebography. She was now cushingoid and had an atrophic skin with maculopapular eruptions in different stages. There were no visible joint deformities but some joint movements were limited. The heart and lungs were normal and there were no palpable lymph glands or any enlargement of the liver or spleen.

**Laboratory studies.** ESR was 103 mm/h. Hb 105 g/l, WBC  $27.5 \times 10^9/l$  with an eosinophilia of 60%, platelet count normal. Serum iron 5  $\mu\text{mol/l}$ , serum transferrin 56  $\mu\text{mol/l}$ , serum vitamin B<sub>12</sub> normal. The bone marrow showed reduced iron deposits and a strongly reactive pattern with predominantly eosinophilic cells. Electrophoresis of the serum revealed a reduced albumin fraction of 75 g/l, increased  $\alpha_1$  and  $\alpha_2$  fractions, elevated haptoglobin and normal gammaglobulins. Serum concentrations of IgG and IgA were normal. IgM was 2.4 g/l (normal

**Abbreviations:** HES=hypereosinophilic syndrome, RF=rheumatoid factor, DECD=dissociated eosinophilic leucocyte disease.

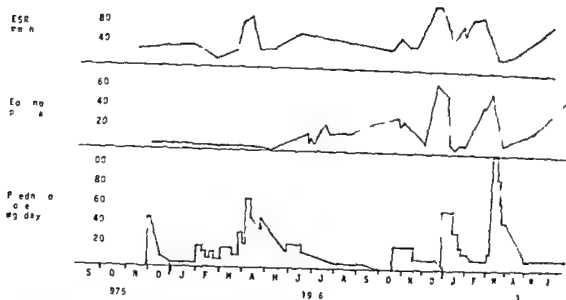


Fig 1 ESR and eosinophilia during treatment with prednisolone

Immunoglobulin G 730 U/ml (normal 16-177). Serum electrolytes were normal. There was no albuminuria or any leakage of proteins into the intestine. The urinary sediment was normal. ASAT and ALAT were normal but LD was slightly raised to 10.5  $\mu$ kat/l (normal 3.8-6.7). The latex test for rheumatoid factor was strongly positive (1/800). Antinuclear factor was negative and plasma C3 and C4 normal but total complement was 55% haemolytic units (CH<sub>50</sub>) (normal range 90-100). Screening of the blood and faeces for signs of any tropical disease gave a negative result. An ECG was unspecifically abnormal with widespread T wave depressions. A muscle biopsy was normal but electromyography showed unspecific myopathy. A skin biopsy revealed vasculitis with thrombosis in the small vessels and infiltrations of mainly eosinophilic cells were seen around the vessel walls. X-rays of the hands showed bony erosions and a reduced amount of cartilage. The picture of arthritis. Chest X-ray showed infiltrations on two occasions and a small exudate on one occasion.

**Treatment and subsequent course.** The patient was treated initially with prednisolone (60 mg/day) and anticoagulant therapy because of the thrombosis. She improved and had less pain from the joints and less pronounced eosinophilia (70%). However a reduction of the steroid dose to 10-15 mg/day repeatedly resulted in serious deterioration with high fever, urticaria, arthralgia and marked eosinophilia (Fig 1). The patient was also treated with a combination of steroids and azathioprine (Imurel®) without any improvement.

In the summer of 1977 she became hoarse, dyspnoeic and very tired. In July 1977 a course of cyclophosphamide (Sendoxan®) was initiated but the general condition gradually deteriorated and the patient died in circulatory and respiratory collapse.

**Autopsy.** The heart was slightly enlarged. A mural

thrombosis was found in the right auricle and a embolus in a pulmonary artery. The liver was enlarged with some fatty infiltration. Old pyknotic scars were found in both kidneys. Microscopically there were some fibrous streaks in the left ventricle and the lungs showed an interstitial chronic pneumonia (usual in elderly pneumonia type) and extensive fibrosis. In the bone marrow there were increased phagocytes with mature cells.

## DISCUSSION

The disease started as typical rheumatoid arthritis in a woman with previous atopic reactions. Her original eosinophilia of about 8 was compatible with this atopy. Eosinophilia to a certain degree is occasionally seen in rheumatoid arthritis (76). However more marked eosinophilia (89%) has also been reported in very severe rheumatoid arthritis with deformed joints and a frequency of subcutaneous nodules and tophaceous and a high titre of RF (19). In our patient pronounced eosinophilia in the blood and throughout the vasculitis and thrombosis and the fatal progress suggest some other reaction in addition to rheumatoid arthritis.

The hyper-eosinophilic syndrome and various manifestations with eosinophilia in blood and bone marrow and in other organs. Many excellent reviews are published (6). Chusid et al (16) found HFS to be a very rare

case with a two-year mortality of 80% regardless of treatment. The HES patients with the poorest prognosis are those with blast transformation in the marrow. Patients with a much longer survival have also been reported (10-21) as well as patients who have responded favourably to steroid therapy. Other syndromes which may be regarded as variants of HES are Loeffler's endocarditis (17, 18, 19) and Churg and Strauss' allergic angitis. The pathological picture in our patient had features in common with the latter disease. The most typical, the granulomatosis, was

The aetiology of HES is still unknown. Immune mechanisms may be responsible for the disease, as an autoimmune phenomenon or as a reaction to an exogenous antigen—or a combination of both. Some authors (9, 18, 20) have named HES 'stimulated eosinophilic collagen disease'. Even though clinical or laboratory evidence of what is generally regarded as a collagen disease has been very sparse. In the previously reported cases of DECD a positive rheumatoid factor has been very rare. Our patient, however, had a very high titre of RF and an extremely low titre indicating an active immunological disease. Another feature of hypereosinophilic states is a tendency towards multiple thrombosis. In our case this was manifested as thrombosis in the leg and later, despite anticoagulant treatment, in a thrombus in the heart and a pulmonary embolism. Ishii et al. (15) wanted in fact to rename this hypereosinophilic multiple thrombosis. This finding was repeatedly made in our patient, namely disseminated vasculitis. Vasculitis is a common complication of rheumatoid arthritis, especially in the presence of high titres of circulating immune complexes (4, 12, 13, 16). Pulmonary fibrosis, which was a striking finding at autopsy, is also well known in rheumatoid arthritis, especially in cases with high titres of immune complexes and is in fact more common in rheumatoid arthritis than was formerly believed (11). It is thought that some immune complexes have an eosinophilic property (7, 22). Thus many of the features in this patient—vasculitis, pulmonary fibrosis, arthritis and pleuritis and possibly the eosinophilia—can be explained by the deposition of immune complexes in various organs. Another interesting feature in this patient was her sensitivity to drugs. Penicillin allergy is common in

many collagenoses, especially systemic lupus erythematosus and Sjögren's syndrome (28). Cases in which a drug reaction has presumably triggered HES have been described (8, 20). An idiosyncrasy for analgesics was also suspected in our patient. Since this kind of hypersensitivity is considered to reflect a direct inhibition of prostaglandin synthesis (24, 27) and thereby a rather unspecific reaction, it might be speculated that such idiosyncrasy will tend to be more common when the immune system is already involved, as in this case, i.e. when the patient's reaction threshold is lower than normal.

In conclusion we consider it possible that in this patient some factor—most probably an immune complex and perhaps identical with RF—stimulated the bone marrow to produce excessive amounts of eosinophils and that this production later became self-regulating, leading to death. The disease might well have been triggered by some drug.

Patients with a malignant form of HES who do not react positively to steroids might benefit from leucopheresis (8). Since immune complexes are probably involved, plasmapheresis might also be tried. This may be of benefit especially if performed in an early stage of the disease.

## REFERENCES

- 1 Benveniste D S & Uhlmann J E. Eosinophilic leukemia. Report of five cases and review of the literature. *Ann Intern Med* 71: 731, 1969.
- 2 Burton J L & Burton P A. Pulmonary eosinophilia associated with vasculitis and extra-vascular granulomata. A case report and review of the literature. *Br J Dermatol* 87: 412, 1972.
- 3 Carrington C B, Addington W W, Goff A M, Madoff I M, Marks A, Schwaber J R & Gaensler E A. Chronic eosinophilic pneumonia. *N Engl J Med* 280: 787, 1969.
- 4 Christian C L & Sergent J S. Vasculitis syndromes. Clinical and experimental models. *Am J Med* 61: 385, 1976.
- 5 Churg J & Strauss L. Allergic granulomatosis, allergic angitis and periarteritis nodosa. *Am J Pathol* 27: 277, 1951.
- 6 Chusid M J, Dale D C, West B C & Wolff S M. The hypereosinophilic syndrome. Analysis of fourteen cases with review of the literature. *Medicine* 54: 1, 1975.
- 7 Cohen S & Ward P A. In vitro and in vivo activity of a lymphocyte and immune complex-dependent chemotactic factor for eosinophils. *J Exp Med* 133: 1971.
- 8 Eilman L, Miller L & Rappaport J.

- sis therapy of a hypereosinophilic disorder JAMA 230 1004 1974
- 9 Engfeldt B & Zetterstrom R Disseminated eosinophilic collagen disease A clinical and pathological study of a clinical entity related to Löffler's syndrome Acta Med Scand 153 337 1956
- 10 Fledelius H Extreme persistent eosinophilia with high serum  $B_{12}$  values A report of two cases Acta Med Scand 187 235 1970
- 11 Frank S T Weg J G Harkleroad L E & Fitch R F Pulmonary dysfunction in rheumatoid disease Chest 63 27 1973
- 12 Glass D Soter N A & Schur P H Rheumatoid vasculitis Arthritis Rheum 19 950 1976
- 13 Gordon D A Stein J L & Broder I The extra articular features of rheumatoid arthritis A systemic analysis of 127 cases Am J Med 54 445 1973
- 14 Hardy W R & Anderson R E The hypereosinophilic syndromes Ann Intern Med 68 1220 1968
- 15 Ishii T Koide O Hosoda Y & Takahashi R Hypereosinophilic multiple thrombosis A proposal of a new designation of disseminated eosinophilic collagen disease Angiology 28 361 1977
- 16 Mongan E S Cass R M Jacox R F & Vaughan J H A study of the relation of seronegative and seropositive rheumatoid arthritis to each other and to necrotizing vasculitis Am J Med 47 23 1969
- 17 Oakley C M & Olsen E G J Eosinophilia and heart disease Br Heart J 39 213 1977
- 18 Odeberg B Eosinophilic leukemia and disseminated eosinophilic collagen disease—a disease entity? Acta Med Scand 177 129 1965
- 19 Panush R S Franco A E & Schur P H Rheumatoid arthritis associated with eosinophilia Ann Intern Med 75 199 1971
- 20 Pierce L E Hosseini A H & Comar B Disseminated eosinophilic collagen disease JAMA 229 540 1967
- 21 Resnick M & Myerson R M Hypereosinophilic syndrome Report of two cases with post courses Am J Med 51 460 1971
- 22 Robert F Omura E & Durant J R M Eosinophilic gastroenteritis with systemic involvement Am J Med 62 139 1977
- 23 Roberts W C Liegler D G & Carver P Endomyocardial disease and eosinophilia A clinical and pathologic spectrum Am J Med 46 29 1969
- 24 Samter M & Beers R F Intolerance to aspirin Clinical studies and consideration of its pathogenesis Ann Intern Med 68 975 1968
- 25 Shepherd A J N Walsh C H Archer R I Wetherley Mein G Eosinophilia, leucocytoclastic cardiac disease Br J Haematol 20 33 1971
- 26 Sylvester R A & Pinals R S Eosinophilic rheumatoid arthritis Ann Allergy 78 465 1970
- 27 Szezeklik A Gryglewski R J & Czerny Mysik G Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin sensitive patients Br Med J 1 67 1975
- 28 Williams B O Onge R A S Young A I G Dick W C & Whaley A Penicillin and rheumatoid arthritis with special reference to greyness syndrome Ann Rheum Dis 74 607 1962
- 29 Yam L T Li C Y, Necheles T F & Yamamoto I Pseudoeosinophilia eosinophilic colitis and eosinophilic leukemia Am J Med 53 1972

## Thanks to Our Referees

is the last number of the Acta Medica Scan-  
za for the decade. The editors want to thank  
referees for all their unselfish and painstaking  
est in discussing the papers before they were

printed. On this limited space I would like to men-  
tion those colleagues among many others during  
the 70s who in the last two years have reviewed  
papers submitted for publication to our journal

as	S Enksson	J Karnell	P Reizenstein
amsson	O Faber	A Kallander	U Ringborg
Almer	U de Faire	S Kistner	A Rosen
qvist	A Forsgren	C Kuhl	E Sandoe
any	H Forsman	J Ladefoged	N Schwartz Sørensen
mann	M H Frick	B A Lamberg	A Sjogren
shven	A K Furhoff	H W Larsen	B Sjogren
eg	F Fyhrquist	N Lassen	F Sjoqvist
Bergentz	A Grubb	C B Laurell	P Stavem
ghund	A Gustafsson	U Lindblom	O Storstein
Bertler	H Gotzsche	J Ljunggren	G Tibblin
Edler	B Hæger Aronsen	B Lown	I Turesson
Emback	D Hallberg	P K Lunde	G Tornell
Berg	T Hallbook	B Lundh	A Vahlquist
ndt	L Å Hanson	P Lund Johansen	H Vallin
chner Mortensen	R Hast	T Lundman	E Varnauskas
Lht	R Hed	R Luft	S Vinblad
Carlson	A Hellem	G Magnusson	J Wahren
elerlof	C Helmers	J Malmquist	A Waldenstrom
enberg	E Hess Thaysen	P Manhem	J Waldenstrom
stedt	J Hess Thaysen	G Matell	O Wegelius
hed	Å Hjalmarsson	E A Nikkila	P O Wester
ulstrom	G Holm	I M Nilsson	L Wibell
ukert	B Hokfelt	L Å Nilsson	H Wynbladh
Dymlung	H Ibsen	S Nitter Hauge	L Wilhelmssen
chag	D Ingvar	F Norbring	F Wollheim
er	B Johansson	G Nuki	H Åberg
lasch	B W Johansson	M Nyman	T Åberg
ner	L Kayser	K Ohlson	Å Ost
Erhardt	B Karlberg	J Poulsen	J Ostman

efforts of our referees have improved the  
y of the Acta to a very high degree and it may  
propriate to quote the famous Swedish author  
Tegner with a slight travesty Where should

we be if they had never been. Their help has been  
invaluable and as we thank them we also wish them  
many happy new years

Jan G Wal

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97  
98  
99  
100

## INVITATION TO DISCUSSION

## Diet, Lipids and Heart Attacks

heart theory or lipid-heart disease theory on certain correlations that have been accepted as valid facts such as the relation between lipids in atherosclerotic heart disease and food ration during the Second World War in certain countries and in some controlled intervention (14 10 13) Osmo Turpeinen one of the proponents of the polyunsaturates for a healthy school of thought recently reiterated this theme in the 1978 International Lecture of the American Heart Association (24) Some clinicians like John McMichael and George Pickering (5) have never found the dietary hypothesis easy to test and have cited pathological or clinical evidence which is brushed aside by the proponents of the lipid-heart theory as flimsy and not pertinent.

It may then be appropriate to look a little closer at the evidence favoring the diet-heart theory. This is more indicated as the final result of the National Heart Project (NPP) has just been published. This project was organized by most of the protagonists of the causal relation between the American diet and the epidemic of coronary heart disease (CHD) in the USA and the West.

One of the main papers often cited as showing a decrease in mortality from circulatory diseases concomitant with a drop in the consumption of fat is the study by Malmros (24) on the relation of nutrition to health during the Second World War where he states that the decrease in mortality from arterio- and atherosclerosis diseases in Finland Norway and Sweden during the years of the war. It is clear that this is associated with a reduced consumption of eggs butter and other foodstuffs rich in cholesterol. As so many other authors linking fat with atherosclerosis diseases did not discuss the wartime rationing of fats and gasoline two other commodities that influence the mortality. Of greater importance is however that he used the crude death rate from atherosclerotic diseases leading to the rather

remarkable fact that Sweden had 50% higher mortality than the USA double that of Finland and three times that of Norway. When you furthermore realize that death certificates in the 40s were signed by laymen in about 20% of deaths and that senility and uncertain causes still made up about 20% of the causes of death the figures for atherosclerotic diseases show up in all their uncertainty. To equate the figures with CHD a disorder not yet clearly defined at that time is also impossible.

Malmros is resting his whole case on the parallelism between mortality from atherosclerosis and fat consumption in each of these countries. That (according to Malmros) the yearly per capita consumption of total fat in the USA varied around 30 kg between 1935 and 1947 corresponding to an increasing death rate from atherosclerosis of 65-120/100 000 population while in Sweden the death rate varied between 125 and 160/100 000 population for a total fat consumption of 17-21 kg per capita during the same years did not lead to any comment from the author or from any of his followers.

Even if the crude death rates were accurate there are still other explanations of the variability. The most probable is that the decrease in atherosclerotic deaths were due to the wartime lack of respiratory epidemics after an influenza epidemic in the late 30s. This coupled with the advent of anti-infectious treatment with the emerging sulfa drugs is quite enough to explain the short time decrease in mortality. To use Malmros' paper of 1950 as any thing more than a curious example of the lack of insight in how to use mortality statistics indicates a marked need for support of the uncertain theory.

Another corner stone in the lipid-heart theory is the straight line relation between serum cholesterol and the later incidence of clinical manifestations of CHD. Repeatedly it has been stressed that the lower the serum cholesterol the lower the risk (2 4 7 9 10 12 14 17 19 21 22 23 24). It has not been possible to define which level of cholesterol should be aimed at but below 200 or even 180 mg/dl has been mentioned (22 23). It is therefore that one of the best documented US



NPP (19) in its final report shows that the standard incidence ratio in all studies and in pool 3 was higher in the lowest quintile of serum cholesterol than in the next. This led the authors to use the two lowest quintiles combined as basal risk. Even the third quintile did not have a much increased risk if compared with the lowest. The final result of this study using fatal and non fatal myocardial infarction and sudden coronary death as end points after 8.6 years of observation in a large sample of men 40-59 years of age, thus shows that serum cholesterol values below 240 mg/dl carry similar risks. Only in the highest quintile is the risk appreciably higher. In an ongoing population study in Gothenburg the risk of myocardial infarction is about the same for the four lowest quintiles of cholesterol and appreciably higher only for the highest quintile (8). This is a finding similar to what is now published by the NPP.

Even though analysed in a variety of ways the lack of linearity between risk and serum cholesterol cannot be obscured. Needless to say the authors—all protagonists of the diet-heart disease theory—do not emphasize this remarkable result but say it should lead to further studies. One of them Stamler (22) in a review article published at the same time as the result of the NPP still uses these figures to emphasize that it is the rich American diet that causes the CHD epidemic in the USA and maintains that the ideal serum cholesterol should be way below 200 mg/dl. He also maintains that there are not enough data to exactly delineate where the upper limit ideally should be. This seems rather negative. The NPP did not show any benefit with serum below 240 mg/dl (19).

#### *Introduction of bias in the studies*

It is understandable that the authors of the many American epidemiology studies of coronary heart attacks usually do not discuss the role of the bias introduced in the studies because of the drop-out problem. It is obvious that the aim of most such studies—as for example the Framingham study and the NPP—is to depict the risk situation for the whole American population at least for its middle aged men. There are however a few who admit that the large amount of non responders in such studies constitute a problem in the interpretation of the results. Such was the case when the Framingham study was planned in the 50s. The effort to

diminish the number of non responders by recruiting families rather than individuals was however not successful and might have introduced a bias instead. Adding some volunteers at a later stage in the sample had shown a response rate of 60% in the same age categories certainly did not improve the representativeness of the sample. The bias of this study which nowadays are published at least each month in some scientific journal are said to represent the white US population but it is not. The same goes obviously for the other studies where Framingham is the only part of the population which has had enough exposure to make an analysis possible. It is interesting to note that Stamler (22) who is probably the most vocal critic of the missionaries for the diet-heart disease now uses the NPP in his main argument. His own study of the Chicago Gas employees has demonstrated that there is very little difference in CHD incidence in relation to the original cholesterol value (final report of the NPP) (18).

There are however a few American studies dressing themselves to the question of bias. In the NHLBI study of twins and lipoproteins the base population in this study was a selected group of veterans in some specific states. Only 17% of the selected twins took part in the study and it was noted that the responders had better education, were better educated than the non responders, and these features are of importance when studying people according to social class in epidemiological studies.

Another study of the importance of exercise is published by Remington et al (20) who used a rather ingenious way of stepwise analysis of who were willing to volunteer for a study to assess the effect of exercise training on coronary risk factors. They concluded that they did not find any correlation between responders and non responders. This was at least partly due to the selection of different population groups studied which were treated somewhat differently. Nevertheless they also concluded that the sample certainly was not representative of the population.

It is of importance to note that bias is a problem in all large American population studies as this is one of the reasons why the results do not check with those from more carefully conducted European studies. One point of special concern is the emerging of social class as a factor in

risk factor in Europe but non-existing in selected American studies

### *Reporting—force of persuasion?*

appreciated enough that the same persons use the same data over and over again create the impression that an enormous wealth of information has been gained over the last few decades. The authors also emphasize that most of what is said supports the diet-lipid heart disease hypothesis. Repetition of statements that are only partly true do not become truer or more scientific by being repeated alone. Look at the Finnish Mental Hospital Study. Two preliminary reports have been published, the last one in 1972 (17). So far, the final report could be critically evaluated has not been made public yet. The final report of the NPP has appeared and gives a different impression, for example serum cholesterol than the published preliminary report (9). The total correlation between sudden death and serum cholesterol in the preliminary report has, however, been omitted. Authors to omit this analysis in the final report are quite a lot of statistical sophistication to analyse the combined feature myocardial infarction, fatal and non-fatal plus sudden death.

Discussion of the diet-heart theory and its implications for preventive measures would not be complete without some comment on the results of the Oslo primary preventive trial using clofibrate. This trial was carried out in Edinburgh, London and Prague on a total of 15745 men aged 40-59 years at the time of entry. The treatment group consisted of a randomly selected half of the men whose serum cholesterol concentrations fell in the upper third of the distribution in about 10000 volunteers tested. The other 5000 men with low cholesterol values received placebo. The control group comprised 5000 men selected at random from the lower kind of the cholesterol distribution. The men were treated for an average of 5.3 years. The reduction in serum cholesterol concentrations in the treatment group amounted to 9%, considerably less than what was achieved (15%). In the groups within the high range of cholesterol concentration, clofibrate made no difference to the incidence of fatal heart attacks, nor was there a significant difference in the incidence of non-fatal myocardial infarcts in

those who received clofibrate. This reduction was greater in men with the higher serum cholesterol values who also showed the greatest reduction in their serum cholesterol concentrations. While this study showed a reduction in non-fatal infarcts, the overall impact of clofibrate on death rate apparently was adverse. Both number of deaths and the crude mortality rates from all causes in the clofibrate-treated groups were significantly higher than in the control group.

An editorial in the British Medical Journal (3) concludes: 'The immediate practical conclusion must be that clofibrate can no longer be recommended as a lipid lowering agent for general use (though it may still have a place in treating specific hyperlipidemias). Furthermore, since there are so many unanswered questions, the other lipid lowering regimens recommended for general use may possibly share the same problems and regimens of this kind—including perhaps dietary modification with polyunsaturated fats—will require equally careful consideration in the future if we are to achieve benefit without at the same time causing more harm than had individuals been left untreated.'

The main arguments for preventive measures against CHD now, before we have solid evidence that these measures will prevent this type of heart disorder, have been: 1) that they do not increase risks and do not entail any risk, and 2) that they are aimed at preventing sudden death, the presentation of CHD that cannot be treated as the victim succumbs within the first hour (2, 21).

If we look more in detail at the arguments for change in diet now, before any evidence is there, it may be that change in diet is without risk for the individual although even this has been questioned (3). It may be another question for the community, especially those societies where agricultural production is of importance both for the economy and for the social welfare of a large part of the population. Without getting too deep into the results of widespread dietary changes for the agricultural industries, it is enough to point out that it is reasonable to have well founded arguments when interfering with a large part of the society regarding work, employment and income.

When it comes to prevention of sudden death, it is quite clear from many studies that about 60-70% of deaths from CHD occur outside hospital and are unattended. This means that this group of

prises about one half to one third of all instances of CHD. At a closer look about two thirds of these deaths have already had some earlier manifestation of the heart disorder—mostly a recognized myocardial infarction. Many studies have demonstrated that the prognosis towards prolonged life in those cases depends on the size of the infarct and the continuation of smoking. Diet or blood lipids are of no consequence for the final outcome in these patients.

Furthermore, if you look at the correlation between the common risk factor and sudden death as the first sign of CHD, for example in the American Pooling Project, there is no straight correlation between serum cholesterol values and sudden death (9). On the contrary, all values below 250 mg/100 ml have the same risk for sudden death and all above 250 the same somewhat higher risk. In contrast to the other risk factors—elevated blood pressure and smoking—serum cholesterol values bear no straight line correlation to the occurrence of sudden death within 10 years (9). The authors who are most interested in promoting diet changes are obscuring what they themselves demonstrate by correlating to all three risk factors, or by correlating serum cholesterol to all new events of CHD. The argument that dietary changes should postpone sudden death has no background even in the best and often quoted American study (9).

It has been shown that at least some  $\beta$  adrenergic blockers diminish the incidence of sudden death after myocardial infarction (25). The clear-cut results with these medicines should be compared to the ambiguous results with diet or lipid lowering.

The repeated demonstration that manipulation of the serum cholesterol value in man does not influence the mortality rate differs considerably from the demonstration that  $\beta$  blocking agents, or at least alprenolol and practolol, do decrease the incidence of sudden death in patients after myocardial infarction and coronary deaths in patients with moderate hypertension. Is there any way of reconciling these different results?

The use of mortality from heart attacks as an end point for an agent possibly acting on atherosclerosis can be criticized. The complex nature of most heart attacks involving pathophysiologic mechanisms both in vessels and myocardium makes it impossible to equate degree of vascular changes with end organ failure. The myocardium, especially under ischemic conditions, may be very

sensitive to catecholamines and adrenergic influences rather than ischemia may lead to the ultimate fatal outcome. All evidence may be interpreted that high cholesterol concentration (highest quintile or upper third) may lead to myocardial infarction which can be postponed through a modest reduction of serum cholesterol.

Death—especially sudden unexpected death—on the other hand bears no relation to serum cholesterol values but is due to sudden catecholamine influence on the heart. It can be protected to some extent by  $\beta$  adrenergic blocking drugs (25). Such a relation takes into consideration the difference between vascular changes and the myocardial changes in conformance with the final results of the clofibrate trial and points to a reasonable continuation of studies on the mode of death after heart attacks (1, 2, 3). It does not give any support to the idea that changes in diet would decrease the incidence of sudden death or fatal myocardial infarction and confirms thus also the results of the trials.

Science is progressing through original hypotheses consisting of formulating and testing hypotheses in adequate surroundings. The recent studies testing the etiology and pathogenesis of heart disease

ischemic heart disease and arteriosclerosis started in a similar way with formulating hypotheses looking for confirmation in laboratory studies. Some testing of these hypotheses has also been done in widespread population studies. Unfortunately, many if not all of these studies in laboratories and populations have lacked a clear definition both of the end points of the studies and the role of the many factors studied. Therefore, such studies have been inconclusive, leaving the leaders dissatisfied and frustrated (1, 4, 6, 17, 21, 22, 24). They have become more and more interested in advocating interference in the way people live as we cannot wait for a scientific proof. (2) The hypotheses to be tested are thus taken over as the most probable hypotheses advocated now is that we should be preoccupied only on the belief of the scientists working in the field (21, 22, 23). Committee reports from various countries or answers to questions may become the most important part of the research to persuade politicians about the need for a new approach.

Scientific results can never be pushed to

a committee or answers to questionnaires  
to resort to compromises arrived at in  
committee meetings by themselves shows the  
strength of the argument for the proposed actions

Lars Werko Sodertälje Sweden

## REFERENCES

- operative trial in the primary prevention of isch-  
emic heart disease using clofibrate *Br Heart J* 40  
1978
- burn H Diet and mass hyperlipidemia: a Public  
reconsideration—A point of view In *Nutrition  
and coronary heart disease* (ed R Levy B  
Dennis and N Ernst) pp 309-347 Raven  
New York 1979
- mal Clofibrate and the primary prevention of  
ischemic heart disease *Br Med J* 115 1585 1978
- me F H Nutrition atherosclerosis and coro-  
nary heart disease: Evidence from epidemiological  
studies In *Atherosclerosis reviews* vol 5 (ed  
Dietrich and A M Gotto Jr) pp 149-187 Raven  
New York 1979
- and atheroma: an inquest (Vane J R p 484  
K G & Betttridge D J p 485 Kay R M  
Fowler P B S p 681 Dobson F E p 682  
A p 687 Trethewey E R p 819 Oliver  
p 889 St George D p 890 McMichael J  
B *Med J* 1979
- rd M Garrison R J Fabsitz R Christan  
Hrubec Z Borhani R H Kannel W B  
man R Schwartz J T & Wagner J O The  
Boston study of cardiovascular disease risk fac-  
tors: methodology and summary of results *Am J  
Epidemiol* 106 284 1977
- k C J & Connor W E Diet-coronary heart  
disease relationships reexamined *Am J Clin Nutr*  
7 1978
- arson Å Werko L & Wilhelmsson L Kost-  
faktors betydelse—kritiska synpunkter II Na-  
turskanning 22 301 1978
- society Committee on Primary prevention of the  
arteriosclerotic diseases *Circulation* 42 A 55 1970
- 10 Keys A (ed) Coronary heart disease in seven  
countries *Circulation* 41 (Suppl) 1970
- 11 Keys A Taylor H L Blackburn H Brozek J  
Anderson J T & Simonson E Coronary heart  
disease among Minnesota business and professional  
men followed fifteen years *Circulation* 28 381 1963
- 12 Levy R J Progress in prevention of cardiovascular  
disease *Prev Med* 7 464 1978
- 13 Malmros H The relation of nutrition to health *Acta  
Med Scand* (Suppl) 46 137 1970
- 14 Mann J I Fat and atheroma: a retinal *Br Med J*  
1 737 1979
- 15 Marmot M G & Syme L S Acculturation and  
coronary heart disease in Japanese Americans *Am J  
Epidemiol* 104 75 1976
- 16 McMichael J Fats and atheroma: an inquest *Br  
Med J* 1 173 1979
- 17 Miettinen M Turpeinen O Karvonen M J  
Elosuo R & Paavilainen E Effect of cholesterol  
lowering diet on mortality from coronary heart dis-  
ease and other causes *Lancet* 2 835 1977
- 18 Olson R E Is there an optimum diet for the preven-  
tion of coronary heart disease? In *Nutrition lipids  
and coronary heart disease* (ed R Levy B Rifkin  
B Dennis and N Ernst) pp 349-364 Raven Press  
New York 1979
- 19 The Pooling Project Research Group Final report of  
the pooling project *J Chronic Dis* 31 701 1978
- 20 Remington R D Taylor H L & Bushkirk E R  
A method for assessing volunteer bias and its appli-  
cation to a cardiovascular disease prevention pro-  
gramme involving physical activity *J Epidemiol Comm  
Health* 32 750 1978
- 21 Rivers J & Payne P Why eating should carry a  
government health warning *Nature* 271 606 1978
- 22 Stamler J Population studies In *Nutrition lipids  
and coronary heart disease* (ed R Levy B Rifkin  
B Dennis and N Ernst) pp 25-88 Raven Press  
New York 1979
- 23 Teger L The fat of the land *Newsweek* July 7 p  
11 1979
- 24 Turpeinen O Effect of cholesterol lowering diet on  
mortality from coronary heart diseases and other  
causes *Circulation* 59 1 1979
- 25 Wilhelmsson C Vedén J A Wilhelmsson L  
Tibblin G & Werko L Reduction of sudden death  
after myocardial infarction by alprenolol *Lancet*  
2 1157 1974

# The very journals for you!

## **Acta Chirurgica Scandinavica**

Editor L. Thorén

8 issues per volume Free supplements Including free subscriptions to the *Scandinavian Journal of Plastic and Reconstructive Surgery* (without suppl.) the *Scandinavian Journal of Thoracic and Cardiovascular Surgery* (without suppl.) and the *Scandinavian Journal of Urology and Nephrology* (without suppl.) Together 17 issues per year

Current volume 146 1980

Sw kr 455 per year incl postage

## **Acta Dermato-Venereologica**

Editor Nils Thyresson

6 issues per volume Free supplements

Current volume 60 1980

Sw kr 190 per year incl postage

## **Acta Medica Scandinavica**

Editor J. Waldenström

6 issues per volume Free supplements

Current volumes 207 208 1980

Sw kr 400 per year (two volumes) incl postage

## **Acta Oto-Laryngologica**

Editor C. A. Hamberger

6 issues per volume Free supplements

Current volumes 89 90 1980

Sw kr 325 per year (two volumes) incl postage

## **Acta Pædiatrica Scandinavica**

Editor R. Zetterström

6 issues per volume Free supplements

Current volume 69 1980

Sw kr 325 per year incl postage

## **Audiology**

Editor Stig Arlinger

4 issues per volume Free supplements

Current volume 9 1980

Sw kr 190 per year incl postage

## **Scandinavian Journal of Infectious Diseases**

Editors Justus Ström and Sten Winblad

Managing Editors Folke Nordbrink and Stellan Bengtsson

4 issues per volume Free supplements

Current volume 12, 1980

Sw kr 190 per year incl postage

## **Scandinavian Journal of Plastic and Reconstructive Surgery**

Editors Bengt Johanson and Hans Hultén

3 issues per volume Free supplements

Current volume 14 1980

Sw kr 200 per year incl postage

## **Scandinavian Journal of Psychology**

Editor Lars Kiebbom

4 issues per volume

Current volume 21/1980

Sw kr 180 per year incl postage

## **Scandinavian Journal of Rehabilitation Medicine**

Editor Olle Hook

4 issues per volume Free supplements

Current volume 12 1980

Sw kr 160 per year incl postage

## **Scandinavian Journal of Rheumatology**

Editors Veikko Lahti and Olof Långren

4 issues per volume Free supplements

Current volume 9 1980

Sw kr 160 per year incl postage

## **Scandinavian Journal of Social Medicine**

Editor Ragnar Berthelsen

3 issues per volume Free supplements

Current volume 8 1980

Sw kr 140 per year incl postage

## **Scandinavian Journal of Thoracic and Cardiovascular Surgery**

Editor Viking Olov Björk

3 issues per volume Free supplements

Current volume 14 1980

Sw kr 200 per year incl postage

## **Scandinavian Journal of Urology and Nephrology**

Editors Åke Frimansson H. Bacht and S. C.

3 issues per volume Free supplements

Current volume 14 1980

Sw kr 200 per year incl postage

## **Uppsala Journal of Medical Sciences**

Editor Gunnar Ågren

3 issues per volume Free supplements

Current volume 85 1980

Sw kr 100 per year incl postage

Swedish subscribers Add V A T to all prices

Free inspection copies on request—write to

The Almqvist & Wiksell Periodical Company  
Box 62, S-101 20 Stockholm, Sweden

# Effect of 24-Hour Somatostatin Infusion on Glucose Homeostasis and on the Levels of Somatomedin A and Pancreatic and Thyroid Hormones in Man

P F Lins, S Efendic and K Hall

From the Department of Endocrinology, Karolinska Hospital, Stockholm, Sweden

In order to investigate whether somatostatin plays a role in the regulation of thyroid hormone secretion we have compared the effects of a 24 h somatostatin infusion on insulin and glucose levels on the one hand with its effect on T<sub>4</sub> and TSH on the other. Furthermore the levels of somatomedin A were determined during the infusion. Somatostatin was infused in control experiments. Cyclic glucose was given as an intravenous bolus of 200 µg by a constant rate infusion of 50 µg/h during the 24 h infusion. Somatostatin suppressed basal insulin and glucose levels as well as insulin responses to meals during the first hour whether somatostatin was given or not. Thereafter T<sub>4</sub> and T<sub>3</sub> levels in the control experiments while they slowly decreased when somatostatin was given. The effect of somatostatin was to suppress the effect of somatostatin was to decrease slowly when somatostatin was given. 24 hours (p<0.05) and 24 hours (p<0.05) on the onset of the infusion. In contrast TSH were not suppressed by somatostatin but basal TSH did not decrease. The suppression of T<sub>4</sub> and T<sub>3</sub> was mainly due to the inhibitory effect of somatostatin on the hypothalamus. Our observation that a low dose of somatostatin decreases peripheral T<sub>4</sub> and T<sub>3</sub> levels indicates that somatostatin plays a role in the regulation of thyroid hormone secretion.

Somatostatin and thyroid hormones inulin  
somatomedin A  
and 206 441 1979

Somatostatin is widely distributed in the body in endocrine like cells and in the islets of the pancreas in the gastrointestinal tract and in the pituitary. There are two types of evidence supporting the idea that the peptide plays a physiologic

role in the islets and in the hypothalamus. Somatostatin suppresses the release of insulin and intestinal hormones (1). Secretion of somatostatin from the pancreas in the intestinal tract could be modified by drugs and hormones as well as by the autonomic system (8, 9, 15). On the other hand whether somatostatin plays a role in the regulation of thyroid hormone secretion

We have therefore compared the effects of a prolonged somatostatin infusion on inulin glucose levels on the one hand with those of thyroxine (T<sub>4</sub>), triiodothyronine (T<sub>3</sub>), reverse triiodothyronine (rT<sub>3</sub>) and thyrotrophin (TSH) on the other. In addition an insight into the effect of the peptide on growth hormone (GH) secretion was gained by following the serum levels of somatomedin A (SMA).

## STUDY POPULATION AND METHODS

Eleven healthy volunteers, three women and eight men aged 23-47 years, participated in this study. All had a normal body weight with in the range of 76-101% of ideal body weight (Table 1). The experiments started at 7 a.m. after an overnight fast with the subjects in a recumbent position. Teflon catheters were inserted into a superficial brachial vein of each arm and kept patent with a slow drip of saline. During the first six hours the subjects were fast. Lunch was served at 1 p.m. dinner at 6 p.m. and an evening meal at 10 p.m. In the somatostatin experiments the peptide was given as a priming dose of 100 µg i.v. at 7 a.m. followed by an infusion of 50 µg/hour during 24 or 25 hours. In the control experiments saline was given alone.

Abbreviations: T=thyroxine, T<sub>3</sub>=triiodothyronine, rT<sub>3</sub>=reverse T<sub>3</sub>, TSH=thyrotrophin, GH=growth hormone, SMA=somatomedin A.

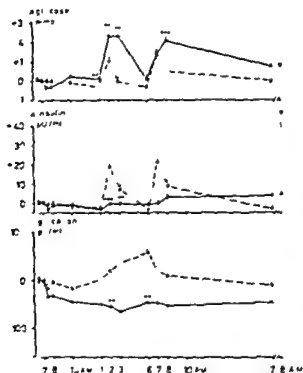


Fig. 1 Effect of somatostatin ( $200 \mu\text{g i.v.} + 40 \mu\text{g/h}$ ) on glucose, insulin and glucagon in healthy subjects ( $M \pm \text{S.E.M.}$ ,  $n=11$ ). Somatostatin was given during 24 hours. In five subjects the infusion was prolonged for one hour.  $\bullet$  — = Experiments with somatostatin.  $\circ$  - - = control experiments. \* $p < 0.05$ , \* $p < 0.01$ , \* $p < 0.005$ .

Blood samples were collected at 6, 7, 8, 10 a.m. at 1, 2, 3, 6, 7, 8 p.m. and at 7 a.m. In five subjects the infusions were prolonged for one hour, and additional blood samples were taken from them one hour after the breakfast at 8 a.m. on the next day. In these subjects hematocrit values were determined throughout the experiments.

Blood glucose was analysed by a glucose oxidase (14) and insulin was measured by a double anti-

body radioimmunoassay technique (11). Plasma  $\text{C}_{50}$  was analysed by a charcoal separation radioimmunoassay technique (10). SMA was determined by radioimmunoassay (12).  $T_4$ ,  $T_3$ , TSH and  $rT_3$  in serum were determined by radioimmunoassays using commercially available reagents (Pharmacia, Uppsala, Sweden).

Cyclic somatostatin was provided by the Research Department of the Kabi Group, Stockholm.

Student's  $t$  test was used in the statistical analysis.

## RESULTS

### Effects on blood glucose, insulin, glucagon and somatomedin A

During the first hour, somatostatin infusion caused a slight hypoglycemia which after transient hypoglycemia turned into hyperglycemia. Simultaneously, basal insulin and glucagon levels decreased. The luncheon and dinner were followed by hyperglycemia which was significantly more pronounced in the somatostatin than in the control experiments (Fig. 1). The hyperglycemia was pronounced two hours postprandially.

The insulin responses to the meals were suppressed by somatostatin. The diabetogenic effect of somatostatin was also evident at the end of the experiments. Thus, fasting glucose levels were significantly increased and the glucose response to the breakfast exaggerated.

SMA remained stable in the control experiments. Somatostatin did not influence SMA throughout the experiments (Fig. 2).

### Effects on $T_4$ , $T_3$ , $rT_3$ and TSH

The levels of  $T_4$  and  $T_3$  decreased during the first hour in the presence and absence of somatostatin (Fig. 3). Thereafter they remained stable.

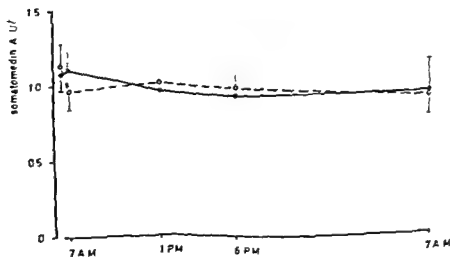
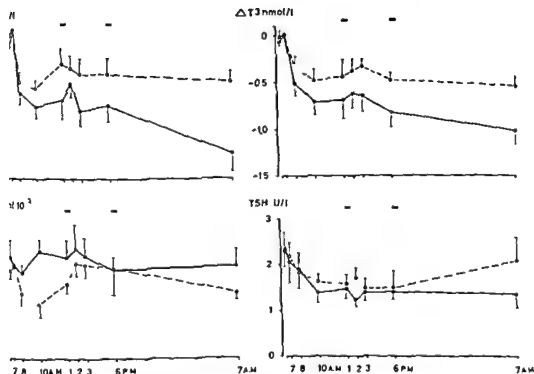


Fig. 2 Effect of somatostatin ( $200 \mu\text{g i.v.} + 40 \mu\text{g/h}$ ) on serum levels of SMA ( $M \pm \text{S.E.M.}$ ,  $n=11$ ). Same subjects as in Fig. 1.



Effect of somatostatin (200 µg i.v. + 50 µg/h) on levels of  $T_4$ ,  $T_3$ ,  $rT_3$  and TSH ( $M \pm S.E.M.$ )

$n=11$  ■=Meals. Other symbols as in Fig. 1 \* $p<0.05$  \* $p<0.01$  \*\* $p<0.005$

experiments while their serum levels decreased slightly when somatostatin was added. The inhibitory effect of somatostatin was significant ( $p<0.05$ ) and 24 hours ( $p<0.005$ ) after the infusion. As demonstrated in Fig. 4, the effect of somatostatin on  $T_4$  and  $T_3$  levels could not be accounted for

by changes in the hematocrit values. In contrast,  $rT_3$  levels were slightly higher in the somatostatin-treated subjects than in the control experiments (Fig. 3).

As expected, TSH was low in the euthyroid subjects (Fig. 3). During somatostatin, TSH seemed to be somewhat lower than during the control experiments but the difference was never significant.



Fig. 4 Effect of somatostatin (200 µg i.v. + 50 µg/h) on hematocrit values ( $Hct \pm S.E.M.$ ,  $n=5$ ). Symbols as in Fig. 1



## DISCUSSION

In the fasting state in humans prolonged administration of somatostatin inhibits basal insulin and glucagon throughout the infusion period (17). It also exerts a slight short lasting hypoglycemic effect which turns into significant hyperglycemia approximately 3 hours after initiation of the somatostatin infusion (17). The present study confirmed these observations and demonstrated that the deterioration in carbohydrate homeostasis induced by somatostatin was even more pronounced in the postprandial situation. Maximal hyperglycemia was attained two hours after the meals.

The hyperglycemic effect of somatostatin was probably at least partially masked by the simultaneous hypoglucagonemia. It was recently demonstrated that restoration of basal glucagon levels during somatostatin infusion by administration of as low a dose of glucagon as 0.5 ng/kg/min significantly enhanced the hyperglycemic effect of somatostatin (16). The same dose of somatostatin as delivered in the present study also suppressed glucagon levels over a 24-hour period in diabetics (5).

In contrast to its prominent effects on insulin and glucagon release, somatostatin did not suppress SMA levels. Since surgical hypophysectomy leads to prompt and significant reduction of somatomedin and since the half life of SMA in serum is about 12 hours (3) this finding implies that somatostatin administration had no major effect on the release of GH in our subjects. This is in accordance with observations by Christensen et al. (5) who were unable to achieve a permanent suppression of GH in diabetics treated with the same dose of somatostatin for 24 hours.

The finding that prolonged *in vivo* administration of somatostatin decreases  $T_4$  and  $T_3$  indicates that the peptide may play a role in the regulation of thyroid hormone secretion. However the site at which its inhibitory action is exerted is not revealed. The lack of effect of somatostatin on basal TSH in this study as well as in many other reports (4, 6, 20) favors the idea of a direct inhibitory effect of somatostatin on the thyroid gland. Weeke et al. (21) who suppressed the nocturnal peak of TSH levels by somatostatin administered the peptide in a dose six times higher than in our study. The idea that a direct inhibitory effect of somatostatin on the thyroid gland is of prevailing importance for the suppression of  $T_4$  and  $T_3$  is further supported by

previous findings that somatostatin inhibits both  $T_4$  and  $T_3$  responses to exogenous TSH *in vitro* (2) and *in vivo* (1, 18).

Since  $rT_3$  and  $T_3$  are mainly formed by conversion of  $T_4$ , the difference between the effect of somatostatin on  $rT_3$  and  $T_3$  might indicate that somatostatin also interferes with the desiodination process. In this context it is of importance that Ahren et al. (1) could not demonstrate effects of somatostatin on the elimination of labelled  $T_4$  and  $T_3$  in mice.

Regardless of how the suppressive effect of somatostatin on  $T_4$  and  $T_3$  is mediated it is obvious from the present study that it is characterized by early onset and that it seems to be permanent.

In conclusion our observation that a low dose of exogenous somatostatin influences the level of thyroid hormones supports the idea that somatostatin may play a role in the regulation of thyroid hormone secretion.

## ACKNOWLEDGEMENTS

This study was supported by grants from the Swedish Medical Research Council (B 76-19X-04540-01), the Insulinfond (Gentofte, Denmark) and Svenska Läkaresällskapets Forskningsfond.

## REFERENCES

- Ahren B, Ericsson M, Hedner P, Ingemansson S & Westgren U. Somatostatin inhibits thyroid hormone secretion induced by exogenous TSH in man. *Clin Endocrinol Metab* 47: 1146, 1978.
- Ahren B, Hedner P, Melander A & Westgren U. Inhibition by somatostatin of mouse thyroid hormone secretion following stimulation by thyrotrophin releasing hormone and dibutyl cAMP. *Acta Endocrinol* 86: 323, 1977.
- Almqvist S & Falkheden T. Studies on somatomedin (SF) activity of human serum. *Acta Endocrinol* 37: 315, 1961.
- Carr D, Gomez Pan A, Weightman D R, Besser G M, Hall R, Besser G M, Thorner M, McNeill A S, Schally A V, Hastin A J & D H. Growth hormone release inhibiting hormone actions on thyrotrophin and prolactin secretion. *Thyrotrophin releasing hormone*. *Br Med J* 3: 6.
- Christensen S E, Hansen Aa, P Weeke, Lundbaek K. 24 hour studies of the effect of somatostatin on the levels of plasma growth hormone, glucagon and glucose in normal subjects and in diabetics. *Diabetes* 27: 300, 1978.
- Copinschi G, Vrasor E, Vanhaelst L, Led R, Golstein J & L Hermite M. Specific inhibition of growth hormone release by somatostatin.

- by somatostatin of growth hormone release after hypoglycemia in normal man *J Clin Endocrinol* 3 441 1973
- Efendic S, Hokfelt T & Luft R. Somatostatin in Metab Disorders 9 367 1978
- Efendic S, Luft R, Roovete A & Uvnas-Wallensten K. Somatostatin release from the pancreas and gastrointestinal tract. *Diabetologia* (Suppl) 14 29 1978
- Efendic S, Nylen A, Roovete A & Uvnas-Wallensten K. Effects of glucose and arginine on the release of immunoreactive somatostatin from the isolated perfused rat pancreas. *FEBS Lett* 97 33 1978
- Faloon G R & Unger R. In *Methods of hormone radioimmunoassay* (ed B M Jaffe & H R Behrman) p 374. Academic Press, New York and London 1974
- Faust C N & Randle P J. Immunoassay of insulin with insulin antibody precipitate. *Biochem J* 88 137 1963
- Feldt A, Brandt J, Enberg G & Fryklund L. Immunoreactive somatostatin A in human serum. *J Clin Endocrinol* 48 271 1979
- Hokfelt T, Efendic S, Hellerstrom C, Johansson J, Luft R & Arimura A. Cellular localization of somatostatin in endocrine like cells and neurons in the rat with special references to the A-cells of the pancreatic islets and to the hypothalamus. *Acta Endocrinol (Kbh)* (Suppl) 80 200 1975
- Kipert A S G & Nixon D A. Use of glucose oxidase, peroxidase and O-dianisidine in determination of blood and urinary glucose. *Lancet* 2 368 1957
- 15 Jupp E, Dobbs E, Harris V, Arimura A, Vale W & Unger R. The effects of gastrin, gastric inhibitory polypeptide, secretin and the octapeptide derivative of cholecystokinin upon immunoreactive somatostatin release by the perfused canine pancreas. *J Clin Invest* 60 1216 1977
- 16 Lins P E, Adamson U, Efendic S & Luft R. Somatostatin effects on glucose homeostasis in man. *Diabetologia* (Suppl) 14 250 1978
- 17 Lins P E & Efendic S. Hyperglycemia induced by somatostatin in normal subjects. *Horm Metab Res* 8 493 1976
- 18 Loos U, Escobar Jimenez F, Raptis S, Brk J, Rothenbuchner G & Pfeiffer E F. Inhibition of TSH induced release of triiodothyronine ( $T_3$ ) and thyroxine ( $T_4$ ) by somatostatin in man. *Acta Endocrinol (Kbh)* (Suppl) 84 208 1977
- 19 Loos U, Voight K H, Kampshoff H, Brk J, Raptis S & Rothenbuchner G. Secretion of  $T_3$  and  $T_4$  by isolated human thyroid cells and its inhibition by somatostatin. *Acta Endocrinol (Kbh)* (Suppl) 50 204 1976
- 20 Siler T M, van den Berg G & Yen S S C. Inhibition of growth hormone release in humans by somatostatin. *J Clin Endocrinol Metab* 37 632 1973
- 21 Weeke J, Hansen Aa P & Lundbaek K. Inhibition by somatostatin of basal levels of serum thyrotropin (TSH) in normal men. *J Clin Endocrinol Metab* 41 168 1975

The  
 12th  
 13th  
 14th  
 15th  
 16th  
 17th  
 18th  
 19th  
 20th  
 21st  
 22nd  
 23rd  
 24th  
 25th  
 26th  
 27th  
 28th  
 29th  
 30th  
 31st  
 32nd  
 33rd  
 34th  
 35th  
 36th  
 37th  
 38th  
 39th  
 40th  
 41st  
 42nd  
 43rd  
 44th  
 45th  
 46th  
 47th  
 48th  
 49th  
 50th  
 51st  
 52nd  
 53rd  
 54th  
 55th  
 56th  
 57th  
 58th  
 59th  
 60th  
 61st  
 62nd  
 63rd  
 64th  
 65th  
 66th  
 67th  
 68th  
 69th  
 70th  
 71st  
 72nd  
 73rd  
 74th  
 75th  
 76th  
 77th  
 78th  
 79th  
 80th  
 81st  
 82nd  
 83rd  
 84th  
 85th  
 86th  
 87th  
 88th  
 89th  
 90th  
 91st  
 92nd  
 93rd  
 94th  
 95th  
 96th  
 97th  
 98th  
 99th  
 100th  
 101st  
 102nd  
 103rd  
 104th  
 105th  
 106th  
 107th  
 108th  
 109th  
 110th  
 111st  
 112nd  
 113rd  
 114th  
 115th  
 116th  
 117th  
 118th  
 119th  
 120th  
 121st  
 122nd  
 123rd  
 124th  
 125th  
 126th  
 127th  
 128th  
 129th  
 130th  
 131st  
 132nd  
 133rd  
 134th  
 135th  
 136th  
 137th  
 138th  
 139th  
 140th  
 141st  
 142nd  
 143rd  
 144th  
 145th  
 146th  
 147th  
 148th  
 149th  
 150th  
 151st  
 152nd  
 153rd  
 154th  
 155th  
 156th  
 157th  
 158th  
 159th  
 160th  
 161st  
 162nd  
 163rd  
 164th  
 165th  
 166th  
 167th  
 168th  
 169th  
 170th  
 171st  
 172nd  
 173rd  
 174th  
 175th  
 176th  
 177th  
 178th  
 179th  
 180th  
 181st  
 182nd  
 183rd  
 184th  
 185th  
 186th  
 187th  
 188th  
 189th  
 190th  
 191st  
 192nd  
 193rd  
 194th  
 195th  
 196th  
 197th  
 198th  
 199th  
 200th  
 201st  
 202nd  
 203rd  
 204th  
 205th  
 206th  
 207th  
 208th  
 209th  
 210th  
 211st  
 212nd  
 213rd  
 214th  
 215th  
 216th  
 217th  
 218th  
 219th  
 220th  
 221st  
 222nd  
 223rd  
 224th  
 225th  
 226th  
 227th  
 228th  
 229th  
 230th  
 231st  
 232nd  
 233rd  
 234th  
 235th  
 236th  
 237th  
 238th  
 239th  
 240th  
 241st  
 242nd  
 243rd  
 244th  
 245th  
 246th  
 247th  
 248th  
 249th  
 250th  
 251st  
 252nd  
 253rd  
 254th  
 255th  
 256th  
 257th  
 258th  
 259th  
 260th  
 261st  
 262nd  
 263rd  
 264th  
 265th  
 266th  
 267th  
 268th  
 269th  
 270th  
 271st  
 272nd  
 273rd  
 274th  
 275th  
 276th  
 277th  
 278th  
 279th  
 280th  
 281st  
 282nd  
 283rd  
 284th  
 285th  
 286th  
 287th  
 288th  
 289th  
 290th  
 291st  
 292nd  
 293rd  
 294th  
 295th  
 296th  
 297th  
 298th  
 299th  
 300th  
 301st  
 302nd  
 303rd  
 304th  
 305th  
 306th  
 307th  
 308th  
 309th  
 310th  
 311st  
 312nd  
 313rd  
 314th  
 315th  
 316th  
 317th  
 318th  
 319th  
 320th  
 321st  
 322nd  
 323rd  
 324th  
 325th  
 326th  
 327th  
 328th  
 329th  
 330th  
 331st  
 332nd  
 333rd  
 334th  
 335th  
 336th  
 337th  
 338th  
 339th  
 340th  
 341st  
 342nd  
 343rd  
 344th  
 345th  
 346th  
 347th  
 348th  
 349th  
 350th  
 351st  
 352nd  
 353rd  
 354th  
 355th  
 356th  
 357th  
 358th  
 359th  
 360th  
 361st  
 362nd  
 363rd  
 364th  
 365th  
 366th  
 367th  
 368th  
 369th  
 370th  
 371st  
 372nd  
 373rd  
 374th  
 375th  
 376th  
 377th  
 378th  
 379th  
 380th  
 381st  
 382nd  
 383rd  
 384th  
 385th  
 386th  
 387th  
 388th  
 389th  
 390th  
 391st  
 392nd  
 393rd  
 394th  
 395th  
 396th  
 397th  
 398th  
 399th  
 400th  
 401st  
 402nd  
 403rd  
 404th  
 405th  
 406th  
 407th  
 408th  
 409th  
 410th  
 411st  
 412nd  
 413rd  
 414th  
 415th  
 416th  
 417th  
 418th  
 419th  
 420th  
 421st  
 422nd  
 423rd  
 424th  
 425th  
 426th  
 427th  
 428th  
 429th  
 430th  
 431st  
 432nd  
 433rd  
 434th  
 435th  
 436th  
 437th  
 438th  
 439th  
 440th  
 441st  
 442nd  
 443rd  
 444th  
 445th  
 446th  
 447th  
 448th  
 449th  
 450th  
 451st  
 452nd  
 453rd  
 454th  
 455th  
 456th  
 457th  
 458th  
 459th  
 460th  
 461st  
 462nd  
 463rd  
 464th  
 465th  
 466th  
 467th  
 468th  
 469th  
 470th  
 471st  
 472nd  
 473rd  
 474th  
 475th

4. Make  
higher  
1 sand

1. The first part of the document is a list of names and titles, including "Jes", "ra", "er", "and", "d", "Spon", "are", "by", "the", "es", "by", "the", "r".

44  
45  
46  
47

# Diagnostic Sign of Hyperglycemia Persistent Movement of Neutrophil Granules

L. Juhlin and W. B. Shelley

From the Departments of Dermatology Uppsala University University Hospital Uppsala Sweden  
and University of Pennsylvania School of Medicine Philadelphia Pennsylvania USA

**ABSTRACT** This study describes a functional test in the blood of diabetics: the motility of neutrophil granules in vitro. When heparinized blood from patients with diabetes mellitus was kept in capillary tubes for 24 hours, a rapid and intense movement of the granules in the neutrophil leucocytes was easily seen. In blood from normoglycemic diabetics and normal subjects, no granular motion was seen after 24 hours, but in these cases prolonged motion could be induced by the prior addition of glucose.

**Key words:** diabetes mellitus, neutrophil granule movement, hyperglycemia.

Acta Med Scand 206 447-1979

Granules of neutrophils are known to oscillate for a short time when viewed free floating under a cover slip. This Brownian movement is less than 1 µm and is often increased in hypotonic solutions. A rapid movement of greater amplitude in a group of granules has also been described. We have studied the movement of granules in neutrophil leucocytes kept in a sealed rectangular capillary tube. The oscillation of granules in blood from healthy subjects and patients with various diseases decreases with time and has usually ceased within 3-8 hours. In patients with diabetes mellitus, however, the movements of granules were still seen after 24 hours.

## MATERIAL AND METHODS

Specimens studied were added (0.01 ml) to one ml of heparinized blood of fasting individuals. Buffy coats were prepared and drawn into fine capillary tubes (Micro-055 Vitro Dynamics, Rockaway, N.J.) sealed and kept at 37°C until viewed under a Leitz phase interference microscope (3).

Compounds added: glucose 0.25, 0.5, 1 and 3 mg in 0.01 ml saline per ml blood; neutral red and toluidine blue 0.1 mg in 0.01 ml saline per ml blood.

## PATIENTS

Thirty patients (ages 40-76) with diabetes mellitus, 8 were treated with insulin, 12 with oral antidiabetics and 10 simply with dietary control of carbohydrate intake.

Forty non-diabetic subjects (ages 25-78) served as controls. They were either healthy hospital personnel or patients with various skin disorders or infections.

## RESULTS

A fine Brownian movement of the neutrophil granules was seen in all the subjects during the first few hours. It was most evident in the cytoplasmic projections, both the protopods and the uropods, which were seen in the moving cells. After 24 hours the movement of granules as seen with 500× magnification had ceased in all controls except in an occasional neutrophil that had phagocytized a red cell. When neutrophils were viewed under higher magnification (1250×), a very slow motion could be detected in the protopods or near the surface of a few neutrophils.

In patients with diabetes and an elevated blood sugar (7.0-20.1 mmol/l) a rapid movement of fine granules was seen after 24 hours (Fig. 1). The granules were moving rapidly around in the whole cell or in certain areas moving around with a greater amplitude than before. The larger granules moved slightly and slowly, reflecting collisions with the smaller ones, as did the vacuoles. The movement was even more evident than at 4-8 hours and was easily seen in most neutrophils even at a magnification of 500×. The movement occurred not only in the cytoplasmic projections but in the w



Fig 1 Three neutrophils with moving granules in blood from a patient with diabetes and hyperglycemia. The thistle-like body is fibrin formation around a monocyte. Such a type of fibrin formation is not seen in diabetes.

regardless of whether they were round or elongated. Many of the neutrophils with intensively moving granules were swollen, which also made the movement easier to detect. The movement could still be seen at 48 hours in some cases.

In the blood of these diabetics, some darkly stained granules could be seen moving during the first hours when neutral red had been added to the blood.

The stain was later seen in the large non-phagocytized granules and vacuoles. The movements of granules in neutrophils having phagocytized neutral red continued unabated. In dead neutrophils, as evidenced by the uptake of toluidine blue, granular movements had ceased. None of the granules of the eosinophil or basophil leucocytes from diabetics were motile at 24 hours.

In four patients with insulin-treated diabetes and normal blood sugar, no movement of the neutrophil granules was seen at 24 hours. Upon the addition of 3 mg of glucose per ml blood, the neutrophil granules showed an intensive movement identical to that seen in hyperglycemic patients. When 1–3 mg of glucose was added per ml blood from controls, granular movement was also present after 24 hours in neutrophils from 28 of 30 non-diabetics. No effect on granular movement was seen after the

addition of only 0.25 mg glucose, but when 0.5 mg glucose was added, a granular movement was seen in neutrophils from 4 of 10 subjects. No effect on the granular movement was seen following the addition of killed bacteria, lipopolysaccharides in saline or water to blood samples.

## DISCUSSION

The main cause of the prolonged movement of granules in the neutrophils observed in patients with diabetes mellitus appears to be hyperglycemia, as the phenomenon could be reproduced in neutrophils by addition of glucose to the blood. Isolation and incubation of the leucocytes. The glucose gives the cells energy to live longer. They probably die more slowly and differently than those with normal glucose levels. The cell membrane changes its permeability and both cell granules seem to take up more water and swell. This makes it easier for the granules and vacuoles to move and be seen. Changing the environment of the neutrophils by the addition of 10% whole saline was not found to influence the movement of granules. Degranulation of neutrophils has been described after exposure to bacterial products (1).

and did not, however, influence the movement of leucocytes in our study. We believe that the granular movement described is unique for diabetes with hyperglycemia as it has been seen while screening over 500 patients without other diseases. This morphological change in the blood of such diabetic patients might be a tool for further studies of diabetes.

#### ACKNOWLEDGEMENTS

For this study was provided by the Swedish Medical Association and the Swedish Medical Research

#### REFERENCES

- 1 Bessis M. Blood smears reinterpreted. Springer Verlag, Berlin, Heidelberg and New York 1977.
- 2 Hirsch J G, Bernheimer A W & Weissman G J. Motion picture study of the toxic action of streptolysins on leucocytes. *J Exp Med* 118: 223, 1963.
- 3 Juhlin L, & Shelley W B. Oriented fibrin crystallization: a phenomenon of hypersensitivity to bacteria. psoriasis, vasculitis and other dermatoses. *Br J Dermatol* 96: 577, 1977.
- 4 Zucker Franklin D. Electron microscope study of the degranulation of polymorphonuclear leucocytes following treatment with streptolysin. *Am J Pathol* 47: 419, 1965.

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

# The Effect of Sulfasalazine and Its Active Components on Human Polymorphonuclear Leukocyte Function in Relation to Ulcerative Colitis

Lars Molin and Olle Stendahl

From the Departments of Dermatology and Medical Microbiology, University Hospital, Linköping, Sweden

**ABSTRACT** Sulfasalazine and its active components 5-aminosalicylic acid (5-ASA) and sulfapyridine (SP) are potent modulators of inflammatory reactions but with somewhat different modes of action. Investigating the effect of these compounds on human polymorphonuclear leukocytes in vitro we show inhibition of different stages in the phagocytic process, such as migration (sulfasalazine and 5-ASA), superoxide production (sulfasalazine and myeloperoxidase mediated iodination and cytotoxicity (5-ASA and SP). It is thus suggested that sulfasalazine is not just a vehicle for delivering its active components in the colon but that its therapeutic effect in ulcerative colitis and other inflammatory diseases is a result of the concurrent action of the components.

**Key words:** polymorphonuclear leukocyte; sulfasalazine; 5-aminosalicylic acid; sulfapyridine; myeloperoxidase; ulcerative colitis.

Acta Med Scand 206 451-1979

Sulfasalazine, formerly known as salicylazosulfapyridine (Salazopyrin<sup>®</sup>, Azulfidine<sup>®</sup>), consists of 5-aminosalicylic acid (5-ASA) and sulfapyridine linked together by an azo bond. The combination of a sulfonamide with a salicylate derivative was introduced by Svartz for the treatment of rheumatoid arthritis and ulcerative colitis (29). The therapeutic effect in ulcerative colitis has been verified by several clinical investigations (4, 11, 12). In rheumatoid arthritis, however, the preparation is ineffective enough.

Although sulfasalazine has been used successfully in clinical practice for more than 30 years, its mode of action is still mainly unknown. It is often regarded as a vehicle for delivering its possible active components to the colon in higher concentrations than could be achieved by oral administration

of either one alone (10, 24). About 70% of the sulfasalazine reaches the colon intact where it undergoes reductive cleavage at the azo linkage, releasing 5-ASA and SP (27). The split is induced mainly by the colonic bacteria (1). All SP is virtually absorbed from the colon, metabolized and then excreted in the urine. Some part of 5-ASA is also absorbed but the main unabsorbed part is excreted in the faeces (24, 27).

Recent investigations have regarded 5-ASA as the active moiety during sulfasalazine treatment. Azad Khan et al. (2) showed that local administration of 5-ASA resulted in a significant improvement in patients with ulcerative colitis, whereas SP had little effect. Nevertheless, the beneficial action of sulfasalazine is far from elucidated.

The present investigation of the effect of sulfasalazine on the function of polymorphonuclear leukocytes (PMNL) was initiated from our earlier observation that dapsone, a sulfone analogue to SP, has a specific effect on the function of PMNL (28) and has been used as a substitute for sulfasalazine, e.g. in M. Crohn (30). Since ulcerative colitis is characterized by an acute mucosal inflammation dominated by PMNL accumulation, the effect of sulfasalazine on PMNL activity was relevant to analyse. Our results reveal that sulfasalazine as well as 5-ASA and SP inhibits different stages in the phagocytic process, such as random migration

**Abbreviations:** 5-ASA=aminosalicylic acid; SP=sulfapyridine; PMNL=poly-morphonuclear leukocytes; KRGR=Krebs-Ringer phosphate buffer containing glucose; FITC=fluorescein isothiocyanate; PBS=phosphate buffered saline; TCA=trichloroacetic acid; STZ=serum treated zymosan; SOD=superoxide dismutase; MPO=myeloperoxidase.

**Reprint requests:** Dr L. Molin, Department of Dermatology, University Hospital, S-581 85 Linköping.



phagocytosis myeloperoxidase (MPO)-mediated iodination oxidative metabolism and cytotoxicity. We thus show that both sulfasalazine and its components are potent modulators of inflammatory reactions but with somewhat different modes of action thereby complementing each other's qualities. These findings are discussed in relation to the therapeutic effect of sulfasalazine in ulcerative colitis as well as in other inflammatory processes.

## MATERIAL AND METHODS

**Leukocyte preparation** Blood was obtained from apparently healthy adult volunteers (age 18–35) and the leukocytes were isolated according to Boyum (5) using Hypaque-dextran sedimentation for the separation of cells from EDTA blood. After separation washing and hypotonic lysis of contaminating erythrocytes the leukocytes were suspended to  $1 \times 10^7$  cells/ml in Krebs Ringer phosphate buffer containing 5 mM glucose (KRG) pH 7.2. A differential count was performed to determine the number of PMNL. Trypan blue exclusion was used to assay viability.

**Motility measurement system** Leukocyte motility was studied by a modification of the method described by Nelson et al. (23). Briefly agarose was dissolved (1.5%) in sterile water by heating. After cooling to 40°C the agarose was mixed with an equal volume of prewarmed Gey's solution in twice its usual concentration. Of the agarose medium 8 ml were poured into 60 × 15 mm tissue culture dishes (Flow Laboratories Irvine Scotland). Six sets of three wells were cut in the agarose. The wells had a diameter of 2.4 mm and in each set they were placed 2.4 mm apart. The drug tested was mixed with the Gey's solution to obtain the same concentration of the drug throughout the agarose.

In each set of wells were placed 10 µl of the cell suspension ( $5 \times 10^5$  PMNL/ml) in the middle well, 10 µl of Gey's solution in the inner well and as an attractant 10 µl of normal serum in the outer well. When normal serum is incubated in the agar chemotactic factors are released (26). To determine random locomotion of the L population both the inner and the outer well was filled with Gey's solution. The dishes were incubated for 2 hours at 37°C. After fixation in methanol for 30 min the agarose was removed and the cells stained with Giemsa for 15 min. The distances of migration were measured with an ocular micrometer.

**Phagocytic uptake** The ability of isolated PMNL to ingest heat killed fluorescein isothiocyanate (FITC)-labelled yeast cells (*Saccharomyces cerevisiae*) was assayed as described by Hed (15). Briefly isolated PMNL were allowed to adhere to glass slides and non adhering cells were removed by washing. To the monolayers were added 0.1 ml of FITC-labelled yeast cells ( $2.5 \times 10^6$  cells/ml) in KRG. The yeast particles were preopsonized with 10 µg/ml of anti yeast IgG. The reaction mixtures were then incubated at 37°C in a humidified chamber. After 30 min the slides were washed and kept in cold (4°C) phosphate buffered saline (PBS) until examined under the mi-

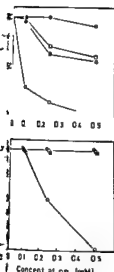
croscope. To separate ingested yeast cells from those attached a drop of crystal violet (0.5 mg/ml in 0.1 M NaCl) was added. The dye stains and thereby extinguishes the fluorescence of the attached particles but does not reach the intracellular ones which still fluoresce combining fluorescence and phase-contrast microscopy. The number of attached and ingested particles is determined. One hundred cells were counted and the phagocytic uptake was expressed as the number of yeast ingested per PMNL.

**Measurement of leukocyte iodination** was essentially as described by Olsson et al. (23). The reaction mixture contained  $1 \times 10^6$  leukocytes, 10% pooled human serum, 30 nmoles of sodium iodide (0.5 µCi of  $^{125}$ I), 1 yeast particle and KRG to a final volume of 0.5 ml. The tubes were incubated at 37°C and the reaction was terminated after 30 min with 0.1 ml of 0.1 M sodium thiosulfate. Five ml of cold 10% trichloroacetic acid (TCA) then added. After centrifugation the precipitate was washed three times with 5 ml of TCA. The iodination was expressed as nmoles I<sup>-</sup> precipitated per  $1 \times 10^6$  PMNL/30 min.

**Superoxide generation** was assayed essentially as described by Cornutte and Babior (9). The reaction mixture contained  $5 \times 10^6$  PMNL, 75 µM horse heart ferrichrome c (Cyt c Type II, Sigma Chemical Co.), serum-treated zymosan (STZ) and KRG to a final volume of 3 ml. The reaction was initiated by incubating the reaction mixture at 37°C in a water bath. 1.5 ml kept at 0°C in melting ice and used as a blank. After 5 min the test tubes were placed in melting ice and the reaction terminated by adding 1.5 ml of 10% TCA. The supernatant was collected and assayed for the amount of reduced Cyt c. Beckman DU 2 spectrophotometer at 550 nm. The amount of reduced Cyt c was calculated using an extinction coefficient of  $15.5 \text{ ml} \cdot \text{cm}^{-1} \cdot \text{mg}^{-1}$  at 550 nm. The superoxide-dependent Cyt c reduction was expressed as the difference in Cyt c reduction between reaction mixtures containing no superoxide dismutase (SOD) (Sigma Chemical Co.) and those containing 200 U/ml. These controls were run with each set of.

**Lysosomal enzyme release** The extracellular release of the PMNL granule associated enzyme  $\beta$ -glucosaminidase (EC 3.2.1.30) in the presence of drugs was assayed from reaction mixtures similar to those employed for the determination of superoxide production but in the absence of Cyt c and using the substrate 4-methyl umbelliferyl 2-deoxy- $\alpha$ -D-glucopyranoside (25). Maximum enzyme release was determined as the amount released by 0.2% Triton (Rohm and Haas Co. Philadelphia Pa.).

**Cell free MPO mediated iodination** MPO isolated from human PMNL was supplied by I. Olsson, Lund, Sweden. The reaction mixtures contained varying concentrations of MPO ( $0.2$ – $10 \mu\text{g/ml}$ ) of yeast cells ( $1 \times 10^6$  nmoles) ( $0.2$ – $10 \mu\text{g/ml}$ ) of MPO,  $1 \times 10^6$  yeast cells,  $1 \times 10^6$  nmoles of NaI ( $1 \times 10^6$  µCi of  $^{125}$ I) and 0.05 M Tris-HCl buffer pH 7.2 to a final volume of 2.0 ml. The reaction was initiated by addition of 0.2 ml of 1 M  $\text{H}_2\text{O}_2$ . After 15 min the reaction was terminated by addition of 0.1 ml of 0.1 M sodium thiosulfate and 5 ml of 10% TCA was added. The precipitate was washed three times with 5 ml of TCA and assayed for radioactivity.



Effect of different concentrations of sulfasalazine (○), 5-ASA (●) or SP (□) on random migration (top) and chemotaxis (bottom). Mean of three experiments.

determine the type of inhibition on MPO-mediated reaction the kinetics of the reaction was studied using different concentrations of iodide (0.05–1.0 mM). The reaction mixture contained 5 µg MPO, iodide (0.5 µCi),  $1 \times 10^6$  yeast cells and Tris HCl to a final volume of 1 ml. The reaction was initiated by addition of 0.2 ml of  $H_2O_2$ .

**$H_2O_2$ -halide mediated cytotoxicity** The cytotoxicity of the MPO  $H_2O_2$  halide system was assessed as described by Clark et al. (8) assaying the  $^{51}Cr$  release from prelabelled mammalian target cells. Human tonsillar lung fibroblasts (WI38 Flow Lab, Irvine, Scotland) were used as target cells. The tumour cells were grown in vitro in plastic Petri dishes (60 × 13 mm, Flow Lab) in Eagle's modified medium supplemented with fetal calf serum and antibiotics. The cells were labelled by incubating them with 25 µCi of  $Na_2^{51}CrO_4$  in KRGB for 1 h. After washing the cells four times in PBS, a reaction mixture was added containing 10 µg MPO, a halide-generating system of 0.5 ml glucose (20 mg/ml), 0.2 ml glucose oxidase (100 µg/ml, E.C. 1.1.3.4, Sigma Chemical Co.) and 0.03 mM sodium phosphate buffer, pH 7.0, supplemented with  $1.5 \times 10^{-3}$  M  $KH_2PO_4$ ,  $10^{-3}$  M  $MgSO_4$ , and 0.1 M NaCl in 3 ml. After 240 min incubation at 37°C, 0.5 ml samples were drawn to test tubes containing 2 ml PBS kept on melting ice and centrifuged at 4°C (250 g, 5 min). The supernatants were collected and assayed for radioactivity. Maximum  $^{51}Cr$  release was determined by counting the supernatants from cells where 0.2% Triton X 100 had been added. The toxicity was expressed as per cent of maximum releasable activity in duplicate samples.

**Reagents** Sulfasalazine, 5-aminosalicylic acid and sulfapyridine (supplied by Pharmacia, Uppsala, Sweden) were dissolved to 1 mM in PBS and kept in the dark at 4°C.

## RESULTS

### Effect of sulfasalazine and its components 5-ASA and SP on PMNL locomotion

The influence of the compounds on PMNL locomotion was assayed with the agarose method according to Nelson et al. (22) using agarose activated serum as chemotactic stimulus.

Sulfasalazine exhibits a pronounced dose dependent inhibition of random migration—0.1 mM decreases the migration to 30% and 0.5 mM abolishes it completely (Fig. 1). The drug has however no effect on the chemotactic response per se since the relative increase in migration in the presence of activated serum was not changed in the presence of 0.1 mM—the decreased motility observed in the chemotactic assay was primarily due to decreased random migration. 5-ASA shows no effect in either random migration or chemotaxis. Neither does SP show any effect at the lower concentration (0.1 mM) most compatible with the concentration reached in vivo. At the higher concentrations (0.25 and 0.5 mM) we observed a moderate but significant inhibition on random migration but no effect on chemotaxis. To evaluate whether the pronounced effect of sulfasalazine is due to the sulfasalazine molecule or to the synergistic effect of 5-ASA and SP the latter compounds were mixed and incubated with the cells. No synergistic effect was however observed—the inhibition was the same as of SP alone (Fig. 1).

### Effect on phagocytosis and metabolic activity

The effects of sulfasalazine, 5-ASA and SP on the phagocytic activity were assayed by counting the number of FITC labelled yeast cells phagocytosed by PMNL attached to glass slides. This method permits an accurate quantitation of the number of ingested and attached particles. Table 1 shows that only sulfasalazine at a high non physiological concentration (0.5 mM) reduced the uptake moderately by 25% ( $p < 0.025$ ), whereas the other metabolites had no significant effect on the phagocytosis of the IgG coated yeast particles.

Phagocytosis of particles by PMNL is accompanied by an increased production of superoxide ( $O_2^-$ ) (9) and hydrogen peroxide ( $H_2O_2$ ) (17). Superoxide,  $H_2O_2$  and their derivatives are thought to play important roles in the microbicidal activity of the cells (3). They may also possess inflammatory mediating properties. Reduction of  $O_2^-$

**Table I** The effect of sulfasalazine (SASP) and its metabolites 5-ASA and SP on PMNL phagocytosis, superoxide production and lysosomal enzyme release

Mean  $\pm$  S.D. range and no. of experiments in parentheses

Supplements (mM)	Phagocytosis*	Superoxide generation <sup>b</sup>	Lysosomal enzyme release <sup>c</sup>
-	3.25 $\pm$ 0.46 (5) (2.83-3.78)	26 $\pm$ 4 (3) (22-29)	100
SASP			
0.5	2.46 $\pm$ 0.10 (5) (2.41-2.56)	16 $\pm$ 5 (3) (11-21)	72 $\pm$ 6 (3) (67-78)
0.1	3.39 $\pm$ 0.52 (3) (2.79-3.92)	24 $\pm$ 6 (3) (17-29)	88 $\pm$ 5 (3) (83-93)
5-ASA			
0.5	3.27 $\pm$ 0.42 (5) (2.48-3.83)	28 $\pm$ 4 (3) (23-32)	87 $\pm$ 9 (3) (81-95)
0.1	3.42 $\pm$ 0.62 (3) (2.81-4.24)	28 $\pm$ 4 (3) (24-33)	87 $\pm$ 6 (3) (83-93)
SP			
0.5	3.08 $\pm$ 0.59 (4) (2.37-4.12)	7 $\pm$ 2 (3) (6-7)	70 $\pm$ 7 (3) (63-76)
0.1	3.20 $\pm$ 0.60 (3) (2.80-3.78)	17 $\pm$ 2 (3) (15-18)	85 $\pm$ 9 (3) (74-95)

\* Expressed as the mean number of yeast particles ingested per PMNL. 100 cells were counted in each duplicate experiment.

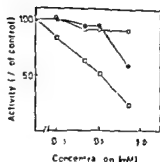
<sup>b</sup> Expressed as SOD-inhibitable  $\text{Cyt c}$  reduction (nmoles of reduced  $\text{Cyt c}/5 \times 10^6$  PMNL, 30 min).

<sup>c</sup> Expressed as % of the enzyme release from PMNL in the absence of drugs.

tion by SOD (20) and other drugs (19) is found to lead to reduced inflammatory response. Table I shows that 0.5 mM of sulfasalazine reduces the superoxide anion production moderately (to 62%). 5-ASA shows no effect, whereas 0.5 and 0.1 mM of SP inhibit the superoxide activity with 75% and 36% respectively ( $p < 0.01$ ).

#### Effect on the MPO mediated iodination

When inorganic iodide is incubated with PMNL during phagocytosis, a portion of the iodide is converted to a TCA precipitable protein bound form. This reaction reflects a complex sequence of reactions related to oxidative activation, internalization, degranulation and MPO activity (18). Fig. 2 shows that sulfasalazine has no significant effect on the MPO mediated iodination. 5-ASA inhibits the iodination reaction only at a high concentration (0.5 mM), whereas concentrations comparable with therapeutic levels have no effect. In contrast, SP exhibits a dose-dependent inhibition even at low



**Fig. 2** Effect of sulfasalazine (O), 5-ASA (●) and SP (▲) on the MPO-mediated iodination in PMNL. Mean of three experiments.

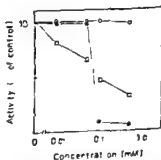
concentrations—0.05 mM inhibits the iodination to 60%.

To further elaborate on the mechanism of inhibition, we studied the effect of 5-ASA and SP on a cell-free system using partly purified MPO. Inhibits the MPO-mediated reaction in a dose-dependent manner, compatible with the inhibition observed in intact cells (Fig. 3). 5-ASA on the other hand inhibits the reaction strikingly at a concentration  $> 0.1$  mM, whereas 0.05 mM has no effect. In kinetic studies using varying concentrations of substrate (0.05–1.0 mM), 5-ASA shows a non-competitive and SP a competitive type of inhibition.

#### Effect on lysosomal enzyme release

The release of the lysosomal enzyme  $\beta$ -N-acetylglucosaminidase was measured after challenge with STZ.

Table I shows that 0.5 mM sulfasalazine reduces the STZ-stimulated lysosomal enzyme release from PMNL to 72  $\pm$  6% ( $p < 0.01$ ) of the controls, whereas 0.1 mM of 5-ASA or SP had no significant effect on this reaction.



**Fig. 3** Effect of sulfasalazine (O), 5-ASA (●) and SP (▲) on the MPO-mediated iodination in cell-free systems. Mean of three experiments.

Effect of 0.2 mM of sulfasalazine (SASP) and SP on the MPO-H<sub>2</sub>O<sub>2</sub> lysis of cytotoxicity of fibroblasts

SD range and no. of experiments in parentheses

Experiments	Cytotoxicity
H <sub>2</sub> O <sub>2</sub> -Cl	48.7 ± 3.5 (3) (46.1–53.6)
H <sub>2</sub> O <sub>2</sub> -C	18.3 ± 2.2 (3) (16.4–20.1)
H <sub>2</sub> O <sub>2</sub> -Cl + SASP	50.0 ± 2.5 (3) (47.3–52.4)
H <sub>2</sub> O <sub>2</sub> -Cl + 5 ASA	32.4 ± 5.2 (3) (27.1–36.2)
H <sub>2</sub> O <sub>2</sub> -Cl + SP	31.9 ± 4.8 (3) (27.2–36.5)

released as <sup>51</sup>Cr radiolabelled cells released of maximum from Triton X 100 (0.2%) treated fibroblasts

hours of incubation

pharmacological concentrations whereas 0.5 mM reduces the release to 70 ± 7% ( $p < 0.01$ )

of the MPO mediated cytotoxicity of fibroblasts

The H<sub>2</sub>O<sub>2</sub> halide system takes part not only in intracellular microbicidal activity of the neutrophil. During phagocytosis both MPO and H<sub>2</sub>O<sub>2</sub> are released into the extracellular fluid and the H<sub>2</sub>O<sub>2</sub> halide system has been reported to be active on certain mammalian cells (18) and may thus initiate the inflammatory process. Using human fibroblasts labelled with <sup>51</sup>Cr as target cells we studied the effects of sulfasalazine, 5 ASA and SP on the H<sub>2</sub>O<sub>2</sub> halide cytotoxic system (Table II). Expected from the inhibitory effect on the MPO mediated iodination both 5 ASA and SP reduce the cytotoxic effect of this system whereas sulfasalazine has no effect. In fact higher concentrations (0.5 mM) of sulfasalazine and 5 ASA seem to render the target cells more vulnerable to the action of the MPO system (not shown by figures).

## DISCUSSION

Although sulfasalazine has been used successfully for many years in the treatment of ulcerative colitis, the inflammatory action is far from understood. In animal models sulfasalazine has been shown to inhibit formaldehyde, dextran and serotonin in-

duced oedema (13–31). Furthermore, the drug can inhibit protease activity (7), some of which is involved in the development of inflammatory reaction by direct tissue damage or by generating chemotactic factors. Sulfasalazine also exhibits immunosuppressive activity by inhibiting delayed hypersensitivity, rejection of skin transplants and lymphocyte cytotoxicity, probably through a toxic action on the effector cell (7–16). Patients suffering from ulcerative colitis often show an elevated number of EAC rosetting B lymphocytes. This elevation is normalized following sulfasalazine therapy (10). There is, however, no effect *in vitro* of sulfasalazine, 5 ASA or SP on phytohemagglutinin responsiveness or rosette formation. In several studies sulfasalazine and its metabolites have been shown to interfere with prostaglandin metabolism, thus influencing the inflammatory reaction. Butt et al. (6) and Gould (14) showed that sulfasalazine and 5 ASA inhibited prostaglandin synthesis. Recently Moore et al. (21) showed that sulfasalazine has an inhibitory effect on prostaglandin E<sub>2</sub> and F<sub>2α</sub> metabolism but a very weak inhibitory effect on prostaglandin synthesis. They also found that neither SP nor 5 ASA was active on the prostaglandin synthesis in concentrations that can be achieved after oral administration of sulfasalazine. The reduction of the elevated prostaglandin levels in the stool of ulcerative colitis patients following sulfasalazine therapy (14) may, however, be secondary to reduced inflammatory response and granulocyte accumulation.

Table III Effect of sulfasalazine (SASP), 5 ASA and SP on different stages in the PMNL function

↓ Pronounced inhibition at pharmacological concentrations  
↘ moderate inhibition on effect at high concentrations of the drugs  
0 no effect

PMNL function	SASP	5 ASA	SP
Migration			
Random	↓	0	↘
Chemotaxis	0	0	0
Phagocytic uptake	↘	0	0
MPO oxidation			
Intracellular	0	↘	↓
Extracellular	0	↓	↓
Superoxide generation	↘	0	↘
Lysosomal enzyme release	↘	0	
Cytotoxicity	0	↓	

Most of these accumulated data point to a general anti-inflammatory action of sulfasalazine and its metabolites. No information is available regarding their influence on the function of PMNL—the major effector cell in the inflammatory response. Several consecutive steps are involved in the PMNL activity. Inhibition of any or some of these steps would result in reduced inflammatory response and tissue damage. In the present investigation we can show that in concentrations comparable to pharmacological doses sulfasalazine, 5-ASA and SP interfere with vital functions of the PMNL, such as migration, superoxide production, MPO-mediated iodination and cytotoxicity (Table III). It is evident that both 5-ASA and SP may modulate the inflammatory response. It is also clear that sulfasalazine (or SP) is not just a vehicle for delivering its active compounds in the colon, as suggested by Azad Khan et al. (2) but may exhibit anti-inflammatory activity in its own right. Although cleavage of the azo bond occurs in the colon, the intact sulfasalazine molecule is absorbed in the upper intestinal tract and serum levels of 0.01–0.1 mM are reached within a few hours (27). These concentrations were found to inhibit random migration *in vitro*.

The effect of SP on MPO activity of PMNL is similar to the effect of dapsone (28)—a sulfone analogue with beneficial anti-inflammatory properties in dermatitis herpetiformis and certain other dermatoses. The clinical effect of SP in the treatment of dermatitis herpetiformis is also nearly as good as that of dapsone. In contrast to dapsone we show that SP also inhibits random migration and  $O_2^-$  production. This may however be due to the higher local concentrations of SP used. The effect of SP on PMNL activity and the beneficial effect of sulfones such as dapsone as an alternative to 5-ASA in Crohn's (30) indicate that the sulfone moiety of sulfasalazine, besides acting as a carrier for the 5-ASA molecule, may contribute to the action of sulfasalazine in the treatment of ulcerative colitis. Furthermore, indirect evidence suggests that sulfones such as dapsone may interfere with the generation of chemotactic factors in certain immune complex-linked dermatoses. We are now pursuing this idea further.

According to the original design of sulfasalazine the intention was to combine an antibacterial and an anti-inflammatory agent (29). In view of the results of the present investigation we rather consider the therapeutic effect of sulfasalazine to be the result of

the concurrent action of the three compounds (sulfasalazine, 5-ASA and SP) with somewhat different and complementary actions on the inflammatory response in the intestinal tract. Whereas sulfasalazine may function systemically and interfere with the recruitment of PMNL to the site of inflammation, 5-ASA and SP could modulate the inflammatory response and tissue damage by interfering with superoxide production, MPO-mediated iodination and prostaglandin metabolism. The effect of sulfasalazine on cutaneous lesions characterized by vasculitis and granulomatous lesions, e.g. pyoderma gangrenosum. However, before a firm explanation can be put forward for the action of sulfasalazine on inflammatory reactions in the intestinal tract, the effect on other cells such as macrophages, eosinophil granulocytes has to be investigated, although the PMNL dominates the lesion description. Above the effect of the drugs on other inflammatory cells such as macrophages, eosinophils and T-cells must be investigated in order to establish the overall action of sulfasalazine.

## ACKNOWLEDGEMENTS

This work was supported by grant 16X 2183 from the Swedish Medical Research Council and grants from the Edvard Welander Foundation, Finsen Foundation and the Swedish Society of Medical Sciences.

## REFERENCES

1. Azad Khan A K, Johnston W H & Trueblood C. Bacterial breakdown of sulphasalazine. *Antonie van Leeuwenhoek* 16: 832, 1975.
2. Azad Khan A K, Pines J & Trueblood S C. Experiment to determine the active therapeutic moiety of sulphasalazine. *Lancet* 2: 892, 1977.
3. Babior B M. Oxygen-dependent microbial killing by phagocytes. *N Engl J Med* 298: 659, 1978.
4. Baron J H, Connel A M, Lennard-Jones J & Jones F A. Sulphasalazine and salicylazosulphadimidine in ulcerative colitis. *Lancet* 1: 11, 1962.
5. Bøyum A. Separation of leukocytes from blood and bone marrow. *Scand J Clin Invest (Suppl)* 97: 196.
6. Butt A A, Collier H O J, Gardner P & Smith S A. Effects on prostaglandin biosynthesis of aspirin affecting gastrointestinal function. *Gut* 15: 344, 1974.
7. Campbell D E S. Internal Pharmacology. Report 1.
8. Clark R A, Klebanoff S J, Eisenstein A & Fefer A. Peroxidase  $H_2O_2$ -halo system. Cytotoxic effect on mammalian tumor cells. *Blood* 45: 161, 1975.

- 16 Crummett J T & Babior B M Biological defence mechanisms. The effect of bacteria and serum on superoxide production by granulocytes. *J Clin Invest* 166: 1974
- 17 K M & Dubin R. Clinical pharmacokinetics of phasalazine. *Clin Pharmacokinetics* 1: 406 1976
- 18 A P Grayson M J Carpenter R G & ne A. Controlled trial of sulphasalazine in the treatment of ulcerative colitis. *Gut* 5: 437 1964
- 19 sanayake A S & Truelove S C. A controlled trial of longterm maintenance treatment of ulcerative colitis with sulphasalazine (Salazopyrin). *Gut* 14: 923 1973
- 20 menjoz R. Antinflammatory effect of salazopyrin. Internal Pharmacia Report 1961
- 21 uld S R. Prostaglandins ulcerative colitis and phasalazine. *Lancet* 2: 988 1975
- 22 J J. The extinction of fluorescence by crystal violet and its use to differentiate between attached and ingested microorganisms in phagocytosis. *FEMS Microbiol Lett* 1: 357 1977
- 23 Im G & Perlmann P. The effect of antimetabolites on the cytotoxicity by human lymphocytes. In: *Advances in transplantation* (ed J Dausset J M Burger & G Mathé) p 155. Munksgaard Copenhagen 1968
- 24 r G Y M Islam M F & Quastel J H. Biological aspects of phagocytosis. *Nature* 192: 535 1972
- 25 banoff S J & Clark R A. Iodination by human polymorphonuclear leukocytes: a reevaluation. *J Lab Clin Med* 89: 675 1977
- 26 meyer J E & Johnston H. Effect of anti-inflammatory drugs and agents that elevate intracellular cyclic AMP on the release of toxic oxygen metabolites by phagocytes: studies in a model of tissue and IgG. *Clin Immunol Immunopathol* 9: 482 1978
- 27 McCord J M. Free radical and inflammation: protection of synovial fluid by superoxide dismutase. *Science* 185: 529 1974
- 28 Moore P K Hoult J R S & Laurie A S. Prostaglandins and mechanism of action of sulphasalazine in ulcerative colitis. *Lancet* 2: 98 1978
- 29 Nelson R D Que P G & Simmons R L. Chemotaxis under agarose: a new simple method for measuring chemotaxis and spontaneous migration of human polymorphonuclear leukocytes and monocytes. *J Immunol* 115: 1650 1975
- 30 Olson O Olofsson T & Odeberg H. Myeloperoxidase mediated iodination in granulocytes. *Scand J Haematol* 9: 482 1972
- 31 Peppercorn M A & Goldman P. Distribution studies of salicylazosulphapyridine and its metabolites. *Gastroenterology* 64: 240 1973
- 32 Peters T J Muller M & de Duve C. Lysosomes of the arterial wall. I. Isolation and subcellular fractionation of cells from normal rabbit aorta. *J Exp Med* 136: 1117 1972
- 33 Repo H. Leukocyte migration agarose test for the assessment of human neutrophil chemotaxis. p 57. Thesis University of Helsinki Finland 1976
- 34 Schroder H & Campbell D E S. Absorption, metabolism and excretion of salicylazosulphapyridine in man. *Clin Pharmacol Ther* 13: 539 1972
- 35 Stendahl O Molin L & Dahlgren C. The inhibition of polymorphonuclear leukocyte cytotoxicity by dapsone—a possible mechanism in the treatment of dermatitis herpetiformis. *J Clin Invest* 62: 214 1978
- 36 Svartz N. Salazopyrin: a new sulfanilamide preparation. *Acta Med Scand* 110: 577 1942
- 37 Ward M & McManns J P A. Dapsone in Crohn's disease. *Lancet* 1: 1236 1975
- 38 Weiss J. Antinflammatory effect of salazopyrin. Internal Pharmacia Report 1965



# The Role of Endogenous Cortisol in Patients with Non-Thyroidal Illness and Decreased $T_3$ Levels

Gunnar Kallner and Jan Gustaf Ljunggren

From Department of Medicine II Södersjukhuset and the Department of Medicine  
St Goran's Hospital Stockholm Sweden

**ABSTRACT** The aim of the study was to elucidate if endogenous cortisol, as previously suggested, could be involved in the mechanism behind the reduced  $T_3$  levels seen in euthyroid patients with various non-thyroidal illnesses. The correlation between serum levels of  $T_3$  and cortisol was investigated in 42 hospitalized patients with non-thyroidal illness and hyperpyrexia. The results showed a correlation coefficient of  $-0.94$  indicating a close reciprocal relation between the two hormones. Cortisol may be one factor associated with the decreased  $T_3$  seen in euthyroid patients with non-thyroidal illness. The results also indicate a close parallelism between the total and free  $T_3$  levels during hyper-

## PATIENTS AND METHODS

Sera from 42 hospitalized patients with fever caused by various non-thyroidal illnesses were analyzed for the levels of  $T_3$ ,  $T_4$ ,  $T_3$  resin uptake ( $T_3U$ ),  $T_4$ -binding globulin (TBG) and cortisol. The material has been described previously (9). Eight patients had to be left out due to lack of serum samples.

$T_3$  and  $T_4$  levels were determined by a radioimmunoassay technique recently described (10). The normal level (mean  $\pm$  S.D.) for  $T_4$  is  $89 \pm 17$  nmol/l and for  $T_3$   $1.77 \pm 0.34$  nmol/l.  $T_3U$  was determined by a commercially available kit (Quanta Count®  $T_3$ , Bio-Rad Lab, Richmond, Calif., USA). Normal range 25-35%. Free  $T_3$  index was calculated according to the formula  $T_3 \times (T_3U)/100$  and free  $T_4$  index similarly  $T_4 \times (T_3U)/100$ . TBG was determined by a commercially available radioimmunoassay kit (RIAgnost®-TBG, Hoechst). Normal range 10-42 mg/l. Cortisol was determined by a commercially available radioimmunoassay kit (Diagnostic Products, Los Angeles, Calif., USA). Normal range at 8 a.m. 150-600 nmol/l.

Body temperature when sample was drawn was referred to either of the following six groups:  $>40.0$ ,  $39.9-39.0$ ,  $38.9-38.0$ ,  $37.9-37.0$ ,  $<36.9$  normal (the latter indicating that the blood sample was collected 2-9 months later when the patient was free from disease).

## RESULTS

The influence of the hormone binding proteins on the levels of  $T_3$  and  $T_4$  at different body temperatures was investigated by determination of the free  $T_3$  and free  $T_4$  indices and TBG levels. The results are shown in Table I. No major differences were found in mean free  $T_4$  index or mean TBG levels at different temperatures. The mean free  $T_3$  index decreased with increasing body temperature as did the mean total  $T_3$  levels previously described (9) indicating a close association between the total

serum triiodothyronine ( $T_3$ ) levels are of importance in euthyroid patients with various acute and chronic non-thyroidal illnesses and after starvation and malnutrition (2, 5, 11). An altered peripheral metabolism of thyroxine ( $T_4$ ) seems to be the most reasonable explanation for these decreased  $T_3$  levels. The triggering mechanism behind the altered metabolism is still unclear (4). We have recently studied a group of 49 patients with non-thyroidal illnesses and decreased  $T_3$  levels. We found that hyperpyrexia was commonly associated with the changes in  $T_3$  (9). The aim of the present study was to further elucidate the mechanism behind the decreased  $T_3$  levels in these patients with special reference to the role of endogenous cortisol levels and the influence of the hormone binding proteins.

**Abbreviations:**  $T_3$ =triiodothyronine,  $T_4$ =thyroxine, TBG=thyroxine binding globulin,  $T_3U$ = $T_3$  resin uptake.



Table I Mean values for serum TBG free  $T_4$  index free  $T_3$  index  $T_3U$  and cortisol at different temperatures

	Body temperature (°C)					
	Normal	<36.9	37.0-37.9	38.0-38.9	39.0-39.9	>40.0
TBG						
n	14	13	23	22	27	6
$\bar{x}$	25.7	25.8	28.4	26.3	26.8	24.8
S.E.M.	0.85	1.16	1.06	1.06	1.00	2.53
Free $T_4$ index						
n	14	13	23	22	25	7
$\bar{x}$	24.8	29.0	25.5	25.0	24.0	27.0
S.E.M.	1.42	2.38	1.21	1.19	1.08	2.80
Free $T_3$ index						
n	14	13	23	22	25	7
$\bar{x}$	0.53	0.43	0.37	0.37	0.30	0.25
S.E.M.	0.05	0.04	0.04	0.04	0.03	0.06
$T_3U$						
n	14	13	23	22	24	7
$\bar{x}$	31.2	32.9	31.1	32.6	32.1	35.2
S.E.M.	0.84	0.95	0.67	0.81	0.72	1.64
Cortisol						
n	14	13	23	22	27	6
$\bar{x}$	435	673	601	830	1005	1275
S.E.M.	57	175	43	83	154	321

and free hormone levels. Correlation coefficient ( $r$ ) = 0.99

The results of the estimation of cortisol levels are also shown in Table I. The correlation coefficient ( $r$ ) between the mean  $T_3$  and mean cortisol levels in the different temperature groups was -0.94.

Thus the results show that the decrease in  $T_3$  levels was not caused by variations in the levels of TBG or binding capacity of the hormone binding proteins. The close reciprocal changes in  $T_3$  and cortisol levels indicate that cortisol may be involved in the mechanism behind the decrease in  $T_3$  levels.

### DISCUSSION

The present results indicate that in addition to a decreased  $T_3$  level during hyperpyrexia a decrease in the free  $T_3$  levels is also seen. This further supports the concept of an altered peripheral conversion of  $T_4$  and not decreased serum protein binding as the mechanism behind the changes.

The triggering mechanism(s) causing the altered conversion is still unclear. Administration of corticosteroids has been shown to inhibit the peripheral conversion of  $T_4$  to  $T_3$  (3, 13). Even if the doses of corticosteroids in these studies were unphysiologically high, an increased secretion of corticosteroids has been one of the factors considered responsible

for the decreased  $T_3$  levels in patients with non-thyroidal diseases (6, 7, 12, 13).

Our previous observation (9) of a close relationship between hyperpyrexia and  $T_3$  together with the observation of a close association between hyperpyrexia and cortisol levels (14) indicates a correlation between  $T_3$  and cortisol. The results from the present investigation demonstrate such a close association. Thus cortisol may be involved in the triggering mechanism.

However, opposing such an involvement of cortisol is the observation that no diurnal rhythm is seen despite a five-fold daily change in  $T_3$  levels (11). Furthermore, it was recently demonstrated that a reduction of  $T_3$  levels was observed in patients with acute myocardial infarction without evidence of increased cortisol levels (8). Myocardial infarction is one of the serious illnesses which is accompanied by decreased  $T_3$ . Therefore, if cortisol is involved in the triggering mechanism, it cannot be the only factor involved.

### ACKNOWLEDGEMENTS

This investigation was supported by grants from Swedish Medical Research Council (no. B79-1954, 12) and the Karolinska Institute.

## REFERENCES

- M Pekary A E Hersman J M & D C Plasma thyrotropin thyroxine and thyronine relationships in man *J Clin Endocrinol Metab* 43 533 1976
- F Suchs M J & Oppenheimer J H Incidence of decreased serum triiodothyronine in patients with non thyroidal disease *J Endocrinol Metab* 41 27 1975
- A Ramsden D B Griffiths R S & E G Effect of a single dose of dexamethasone on serum concentrations of thyroid hormones *J Clin Endocrinol Metab* 25 58 1976
- I J Chopra U Smith S R Rezna M & n D H Reciprocal changes in serum concentrations of 3,3',5'-triiodothyronine (rT<sub>3</sub>) and 3,5'-diiodo-L-thyronine (T<sub>2</sub>) in systemic illness *J Clin Endocrinol Metab* 41 1043 1975
- I J & Smith S R Circulating thyroid hormone and thyrotropin in adult patients with protein malnutrition *J Clin Endocrinol Metab* 40 221 1975
- I J Williams D E Origazzi J & Solo-H Opposite effects of dexamethasone on concentrations of 3,3',5'-triiodothyronine and 3,5'-diiodo-L-thyronine (T<sub>2</sub>) *J Clin Endocrinol Metab* 41 911 1975
- L J & Hoye K Dexamethasone suppresses serum T<sub>3</sub> and T<sub>4</sub> *J Clin Endocrinol Metab* 40 221 1975
- en J G Falkenberg C & Savidge G The influence of endogenous cortisol on the peripheral conversion of thyroxine in patients with acute myocardial infarction *Acta Med Scand* 205 267 1979
- 9 Ljunggren J G Kallner G & Tryselius M The effect of body temperature on thyroid hormone levels in patients with non thyroidal illness *Acta Med Scand* 202 459 1977
- 10 Ljunggren J G Persson B & Tryselius M Rapid simultaneous radioimmunoassay for measurement of triiodothyronine and thyroxine in unextracted human serum *Acta Endocrinol (Kbh)* 81 487 1976
- 11 Portnau G I O Brian J T Burk J Vagenakis A G Azizi F Arky R A Ingbar S H & Braverman L E The effects of starvation on the concentration and binding of thyroxine and triiodothyronine in serum and on the response to TRH *J Clin Endocrinol Metab* 39 191 1974
- 12 Wartofsky L Burman K D Dimond R C Noel G L Frantz A G & Earl J M Studies on the nature of thyroidal suppression during acute falciparum malaria Integrity of pituitary response to TRH and alterations in serum T<sub>3</sub> and reverse T<sub>3</sub> *J Clin Endocrinol Metab* 44 85 1977
- 13 Westgren U Ahren B Burger A Ingemansson S & Melander A Effects of dexamethasone desoxycorticosterone and ACTH on serum concentrations of thyroxine 3,3',5'-triiodothyronine and 3,5'-diiodo-L-thyronine *Acta Med Scand* 202 89 1977
- 14 Yamamoto M & Matsui N Effects of changes of body temperature on serum cortisol fractions *Nippon Naibunri Gakkai Zasshi* 54 187 1978

Table I *Diagnosis of acute DVT Comparison between phlebography and thermography (N=55)*

	Phlebography	
	Pos	Neg
Thermography		
Pos	19	3+5 susp
Neg	1	27

Agreement 84%

*Venous plethysmography*

This was carried out with an air filled plethysmograph as described by Dohn (9) and modified by Graf and Westerstam (10). Venous volume was defined as the increase in calf volume 2 min after application of a proximal venous occlusion pressure of 60 mmHg. Venous outflow capacity was defined as the rate of the decrease in calf volume after release of a venous occlusion pressure of 60 mmHg and determined from the steepest part of the slope in the record curve.

*Phlebography*

Ascending phlebography was performed according to Greitz (11).

## RESULTS

An acute thrombosis was diagnosed by thermography in 22 cases and 5 thermographic pictures aroused suspicion of thrombosis. Phlebography demonstrated an acute DVT in 20 patients and in only one of these the thermography was negative. Thus an agreement of 84% was achieved (Table I). The difference between the two methods was 3 false positive thermographies in 3 cases and a false negative thermogram in one case of the 3 patients with false positive thermograms had recently been meniscectomized and one had generalized arthritis. Three of five patients with suspected false positive thermograms suffered from gonitis, local thrombophlebitis and a later visible hematoma respectively. In one case the thermogram became negative after 24 hours and one patient developed a positive thermography after phlebography. It is evident that in 6 of these 8 patients the temperature rise could easily be explained by other clinical conditions than acute DVT. The only patient with false negative thermogram had previously suffered from repeated throm-

bosis and the phlebogram showed a small thrombosis in one of the calf veins.

In 10 cases, thermographically diagnosed as localized thromboses, phlebography showed that the thrombus also occupied part of the femoral vein (10 localized thromboses). Six high and 3 low thromboses were localized similarly by thermography and phlebography, constituting an agreement in localization of 47%.

Table II compares the diagnostic accuracy in localizing ability of phlebography and a combination of thermography and plethysmography. With the diagnostic agreement between phlebography and the thermo-plethysmographic combination was estimated to 83% and was thus on the same level as that between phlebography and thermography alone. The agreement between localization of phlebography and the thermo-plethysmographic combination was 95%.

## DISCUSSION

This study was designed to compare the accuracy of the noninvasive methods thermography and plethysmography with phlebography in the diagnosis of deep venous thrombosis. Our results demonstrate an overall diagnostic agreement of 84% between thermography and phlebography. This is consistent with previous documentation (4, 7 & 15). It should be noted that the incidence of thrombosis in this study was as low as 36%. Thus the suspicion of acute DVT at the clinical examination could not be confirmed by objective diagnostic methods in 64%. Besides illustrating the unreliability of the clinical diagnosis of acute DVT this study

Table II *Diagnosis and localization of acute DVT Comparison between phlebography and a combination of thermography and plethysmography (N=10)*

	Phlebography		
	Pos		Neg
	High	Low	
Thermography and plethysmography			
Pos high	15	1	3+5 Susp
Pos low	-	3	74
Neg	-	1	

Diagnostic agreement 83% localizing agreement 95%

need for simple screening procedures with a sensitive sensitivity. Out of 28 cases with phlebography 27 (96%) also had a negative thermography. The only case of false negative

diagnosis was a patient with several thrombotic episodes and a small acute calf thrombus. The frequency of false negative results with thermography was thus only 2%. This confirms the results in prior investigations regarding the reliability of thermography in detecting the presence of an acute DVT (7-8).

On the other hand, a positive thermographic result with negative phlebography seems to be very frequent. Thus 21 (8%) false positive thermograms have been reported in other studies (5). Several inflammatory conditions such as superficial thrombophlebitis, erysipelas, cellulitis, arthritis and tendovaginitis are known to cause a temperature rise located to the affected limb, which could lead to a false positive thermographic diagnosis (4, 8, 15). We report 3 clearly and definitely false positive thermographies, but in these 8 patients had a clinical picture which could explain the rise of leg temperature and could not be diagnosed. This emphasizes the need for a clinical examination as a basis for the localization of the thermogram.

The localization of an acute thrombosis is important for the choice of therapy in many cases depending on the extension of the thrombus. Thus, if the thrombosis is limited to the calf or popliteal veins, local thrombolytic therapy should be considered. In cases of high thrombosis extending to the femoral vein, our investigation showed that thermography incorrectly diagnosed a low thrombosis in 63% of cases. Phlebography showed a high thrombosis consistent with the finding of Bergqvist (1).

In order to improve the localizing ability it was decided to combine thermography with plethysmography, a noninvasive method with well documented ability to diagnose DVT affecting the venous outflow capacity of the popliteal and/or femoral veins (1-5). We found that this noninvasive technique could both diagnose and localize acute DVT with a high degree of confidence. The agreement between localization by phlebography on the one hand and the combination of thermography and plethysmography on the other

Our results indicate that in the 27 patients with both negative phlebograms and thermograms phlebography was not required for diagnostic purposes. In 6 of the 8 patients with false positive thermograms and with obvious clinical findings explaining the temperature rise, phlebography might also have been omitted. Phlebography can then be reserved for patients in whom thermography and plethysmography do not give conclusive results and in whom thrombolytic therapy is considered—only a minority of patients according to our experience. For this reason we estimate that up to 3/4 of our patients could have been spared from phlebography. In our opinion the noninvasive combination of thermography and plethysmography could to a considerable extent be used as an alternative to phlebography in the routine diagnosis of acute DVT.

## ACKNOWLEDGEMENT

This investigation was supported by a research grant from the Swedish Medical Research Council (no. 14 X 1019).

## REFERENCES

1. Ahlback S, Bygdeman S & Watz R. The value of venous plethysmography in the diagnosis of venous thrombosis and for evaluation of therapeutic results. *Standardization of cardio-angiologic methods* 4: 54, 1977.
2. Albrektsson U & Olsson C-G. Thrombotic side effects of lower limb phlebography. *Lancet* i: 723, 1976.
3. Barnes R W, Wu K K & Hoak J C. Fallibility of the clinical diagnosis of venous thrombosis. *JAMA* 234: 605, 1975.
4. Bergqvist D, Elfving O & Hallböök T. Thermography: A non-invasive method for diagnosis of deep venous thrombosis. *Arch Surg* 112: 600, 1977.
5. Bergqvist E, Bergqvist D, Bronge A, Dahlgren S & Hallböök T. Diagnosis of venous thrombosis in the lower limbs: A comparative study between <sup>251</sup>I-fibrinogen test, strain gauge plethysmography and phlebography. *Ups J Med Sci* 78: 191, 1973.
6. Bygdeman S, Arckberg S & Händmarsh T. Venous plethysmography in the diagnosis of chronic venous insufficiency. *Acta Chir Scand* 137: 423, 1971.
7. Bystrom I O, Larsson T, Lundell I & Åhrom P E. The value of thermography and the determination of fibrin-fibrinogen degradation products in the diagnosis of deep vein thrombosis. *Acta Med Scand* 202: 319, 1977.
8. Cooke J D & Licher M J. Thermography of deep vein thrombosis. *Br Med J* 1973.

- 9 Dohn K. Plethysmographs usable during functional states recording volume changes in ml per 100 ml of extremity. *Rep Steno Hosp (Kbh)* 6: 147. 1956
- 10 Graf K & Westersten A. Untersuchungen über Eigenschaften und Verwendungsmöglichkeiten eines flexiblen Extremitäten Plethysmografen. *Acta Physiol Scand* 46: 1. 1959
- 11 Greitz T. The technique of ascending phlebography of the lower extremity. *Acta Radiol* 42: 421. 1954
- 12 Haeger K. Den kliniska trombodiagnostikens (o) tillförlitlighet. *Läkartidningen* 62: 1067. 1965
- 13 Kakkar V V. Deep vein thrombosis. Detection prevention. *Circulation* 51: 8. 1975
- 14 Leiviskä T & Perttala Y. Thermography in nosing deep venous thrombosis of the lower. *Radiol Clin* 44: 417. 1975
- 15 Ritchie W G M, Soulen R L & Lapayowke S. Thermographic diagnosis of deep venous thrombosis. *Invest Radiol* 12: 404. 1977

# Non-Invasive Methods in the Evaluation of Obliterative Disease of the Subclavian or Innominate Artery

Stig Ekeström Brita Eklund Lars Liljeqvist and Otto Nordhus

*From the Departments of Clinical Physiology and the Thoracic Surgical Clinic  
Karolinska Hospital Stockholm Sweden*

**ABSTRACT** The preoperative investigation of 25 patients referred for evaluation of subclavian artery stenosis is reported. Non-invasive methods were used in addition to angiography to assess arm circulation, direction of blood flow in the vertebral artery, retrograde flow in one vertebral artery was found in 18 patients but only 7 had symptoms judged to be caused by the reversal of flow. In only one case was the arm circulation so impaired as to require the diagnosis of arm claudication. A high frequency of carotid lesions was found on the angiogram.

The report demonstrates that in cases of subclavian steal and/or arm claudication non-invasive methods should be used to screen the patients before surgery. In many cases it will be found that the symptoms cannot be attributed to steal or impairment of the arm circulation and therefore angiography is not indicated. However, in some cases signs of a carotid lesion may still necessitate an angiogram.

**Key words:** non-invasive diagnosis, subclavian artery stenosis, occlusion, obliteration, subclavian steal.

Acta Med Scand 206 467 1979

Obliterative disease of the subclavian or innominate artery may lead to altered hemodynamics to the arm and brain. A significant stenosis or an occlusion of the subclavian artery will cause a decrease in the perfusion (BP) distal to the obliteration and the capacity of the arm may be impaired. Fatigue or ischemic pain during arm work and decreased sensitivity to cold has also been described.

The blood flow in the vertebral artery may be decreased especially during arm work (Fig. 1). In addition a steal of blood flow from the brain

has been assumed (4, 11, 17) which might elicit a vertebrobasilar ischemia with symptoms such as vertigo, visual disturbances, ataxia, contralateral motor and sensory disturbances, headache and drop attacks (14, 16).

During the last 15 years more than 90 patients have been operated on for obliterative disease of the subclavian or innominate arteries at the Thoracic Surgical Clinic, Karolinska Hospital (12). However, a still greater number have been referred for evaluation for the disease. According to our experience as well as that of others (2, 14), in many of the patients the symptoms cannot be ascribed with certainty to the subclavian obliterations and often a coexisting carotid lesion is the more likely cause.

We investigated 25 patients by non-invasive and invasive methods to elucidate how often the above mentioned symptoms can be ascribed to the subclavian stenosis or occlusion. The question is of practical importance since if the symptoms are not related to an obliteration, operation should not be considered and angiography not performed. The findings were considered to indicate operation in 8 of our patients and the results of the operation were subsequently evaluated.

## PATIENTS

The study comprises 25 patients: 17 men and 8 women, average age 60 years (range 42-71). All had a difference of at least 20 mmHg between BPs in the arms.

Twelve patients were referred to hospital because of cerebral symptoms such as vertigo, visual disturbances, drop attacks, fits of motor or sensory disturbances in the arm or leg contralateral to the arm with lower BP. Four of these patients also had symptoms from the ipsilateral arm such as sensitivity to cold in one case and paresthesia in three cases (group I).

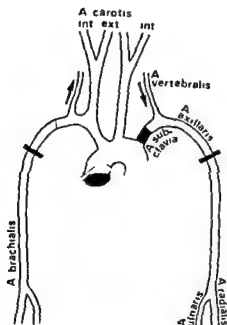


Fig 1 Flow directions in a subclavian steal

Five patients were referred for evaluation of arm symptoms. Two of them had healing gangrenous ulcers in one or two fingers, one complained of continuous pains in her arm and had motor disturbances, one had attacks of pains from shoulder to hand at rest and in one patient arm work induced pain and the hand was extremely sensitive to cold (group II).

Eight patients were referred solely because of difference in BP between the arms and had neither cerebral nor brachial symptoms (group III).

## METHODS

### General investigation

The general investigation comprised a thorough penetration of the symptoms. Peripheral pulses and BP were from both arms. In most cases chest X-ray and bicycle exercise test with ECG recordings formed in addition.

### Direction of vertebral artery flow

Blood flow direction in the vertebral arteries was assessed with Doppler ultrasound as described elsewhere at rest in the sitting position (13). A Parks Electronics Directional flow meter 806 C with a pencil or flat probe of 5 or 10 mHz was used. The probe was held by the hand against the skin over the vertebral arteries below the transversal processes of the atlas vertebra and the flow direction could be read directly from the equipment.

### Arm circulation

Oscillometry was performed with a volume-calibrated Bocke-Brecht infracton oscillograph (1). Arterial pulses were recorded at the upper arm at the largest

circumference of the forearm at the wrist and for comparisons at the largest circumference of the calf.

Systolic BP was recorded from the third finger with strain gauge according to Gundersen (7). A then placed proximally to the gauge. Systolic pressure the arm was recorded with a cuff placed around the arm and the finger gauge was used for detection of pulse. This pressure corresponded closely to pressure determined by the Korotkoff technique.

Forearm blood flow was measured by venous occlusion plethysmography using an air-filled plethysmograph (6) with the patient in supine position. Recordings made at rest and as soon as possible (within 10 sec) maximal forearm work (see below).

Forearm work was performed dynamically on a loaded hand ergometer where the load the length and number of the springs (9). The initial was 1.25 W (7.5 kpm/m) and it was increased 1.25 W every 4th min until the patient stopped because of fatigue. The work load at break point  $W_{max}$  was later the highest load tolerated for 4 min being given by a fraction proportional to the work time at the 1st load.

### Angiography

An angiography was performed in 21 patients. The technique used at this clinic has been described earlier (12). Some patients angiography had been performed at admission.

### Operative technique

The subclavian and innominate arteries were reconstructed by endarterectomy through a thoracotomy. Reconstructions on the internal carotid performed by endarterectomy using an extraluminal connected to an electromagnetic flow meter (3).

## RESULTS

### Group I (cerebral symptoms)

#### Arm circulation (Table 1)

The systolic pressure in the diseased arm was reduced to  $68 \pm 14\%$  of that of the control and the distal pressure (dig III) to  $68 \pm 17\%$ . Oscillometric amplitudes over the upper arm were reduced to  $47 \pm 11\%$  and over the forearm to  $52 \pm 14\%$ . Neither working capacity nor blood flow at rest and shortly after work differed significantly between the arms, thus  $W_{max}$  of affected arm was  $77 \pm 27\%$  of the contralateral postexercise forearm blood flow was  $95 \pm 25\%$ . Four patients who had symptoms also from the other arm did not differ from the other eight with pressure difference, oscillometry work or postexercise forearm blood flow. Arm the diseased arm did not provoke cerebral symptoms in any of the patients.

**Table 1** Ratio affected arm/contralateral arm with regard to oscillometric index, systolic pressure (strain working capacity ( $W_{max}$ ) and postexercise forearm blood flow in the three groups of patients (mean)

	Group I (n=12)	Group II (n=5)	Group III (n=8)
oscillometric index			
upper arm	0.47±0.11	0.39±0.19	0.55±0.15
forearm	0.52±0.14	0.44±0.23	0.65±0.17
postexercise	0.57±0.24	0.44±0.20	0.66±0.19
systolic pressure			
upper arm	0.68±0.14	0.63±0.10	0.71±0.08
forearm	0.68±0.17	0.61±0.20	0.74±0.08
postexercise	0.77±0.27	0.57±0.27	0.89±0.22
postexercise forearm blood flow	0.95±0.25	0.66±0.28	0.90±0.19

#### ultrasound examination

Reversed flow in the vertebral artery on the diseased side was found in 11 patients. In one patient the direction was normal on both sides in spite of a difference of 35 mmHg in BP between the arms.

#### angiography

Angiograms were examined. Complete occlusion of the vertebral artery on the diseased side with retrograde flow in the vertebral artery was found in 9 patients. Six patients had occlusion of the left subclavian artery, one of the right subclavian and two of the innominate arteries. One of the patients with occlusion of the left internal carotid artery had a hemodynamic non significant stenosis in the innominate artery. A total stenosis (left subclavian artery) was found in three patients, and two of them had reversed flow in the vertebral artery. Vertebral flow direction was in agreement with that recorded by Doppler ultrasound technique in all cases. Carotid lesions contralateral to the subclavian or innominate artery obstruction or bilateral were demonstrated in three patients.

#### Indication for surgery and results of therapy

Reversed vertebral blood flow alone was assumed to cause the symptoms in three patients and the innominate artery was then reconstructed. One patient developed an ipsilateral hemiplegia postoperatively, while the other two achieved complete symptomatic relief. Retrograde vertebral blood flow in combination with embolization from innominate or carotid lesions were suspected of giving

rise to the symptoms in four patients. In two of these complete symptomatic relief was obtained after simultaneous reconstructions of the innominate and ipsilateral internal carotid arteries. In a third patient arm and most cerebral symptoms were relieved after reconstruction of the left internal carotid artery but as some vertigo persisted the right subclavian artery occlusion causing retrograde vertebral blood flow was reconstructed one year later whereupon complete relief was obtained. In the fourth patient reconstruction of an innominate artery lesion relieved eye and arm symptoms but as vertigo still persists he is now waiting for reconstruction of an occlusion of the left subclavian artery causing retrograde vertebral blood flow. Complete relief of cerebral and arm symptoms was obtained in two patients after reconstruction of internal carotid lesions contralateral to the subclavian artery obstructions. In three patients neither retrograde vertebral blood flow nor carotid lesions could explain the symptoms and these patients were not operated on.

#### Group II (brachial symptoms)

##### Arm circulation (Table I)

The systolic pressure in the diseased arm was reduced to 63±10% of that of the contralateral and the distal pressure (digit III) to 61±20%. Oscillometric amplitudes were reduced to 39±19 and 44±23% over the upper arm and forearm respectively. Working capacity and postexercise forearm flow were reduced to 57±27 and 66±28%.



tively. In one patient systolic pressure was reduced to 50% and oscillometric amplitudes to 25%. The working capacity of the diseased arm was reduced and clearly limited by ischemic muscle pain. Post exercise blood flow was low in relation to the work performed.

#### *Doppler ultrasound examination*

Three of the five patients were examined and were all found to have reversed flow in the vertebral artery on the diseased side.

#### *Angiography*

All patients were examined. The left subclavian artery was occluded in two patients and stenosed in one. In two patients the right subclavian artery was completely or partially occluded distally to the vertebral artery. In two patients with a left sided lesion where the vertebral artery was visualized, flow direction was in agreement with that found at ultrasound examination. No pathological changes were found in the carotid arteries.

#### *Selection for surgery and results of therapy*

The patient with arm claudication was operated on for an occlusion of the left subclavian artery. Post operatively arm BP, oscillometric indices, working capacity and postexercise blood flow were normalized. Two patients had healing ulcers on their fingers and were already on anticoagulant therapy. They had a stenosed subclavian artery with a moderate pressure difference between the arms. The lesions were due to embolization from the stenosed part of the vessel. These patients were not operated on. The ulcers healed and no new embolic episodes occurred. In one patient with a moderate arm pressure difference, angina pectoris was the cause of her arm pains, which were relieved by nitro drugs, and in another an X ray damage of the brachial plexus explained her pains and motor symptoms.

#### *Group III (without symptoms)*

##### *Arm circulation (Table I)*

The systolic pressure in the diseased arm was reduced to  $71 \pm 8\%$  of that of the contralateral and oscillometric amplitudes over the upper arm to  $55 \pm 15\%$ , i.e. to the same order of magnitude as in group I. Working capacity and postexercise blood flow were not significantly reduced in the affected arm compared to the contralateral.

#### *Doppler ultrasound examination*

Six of the eight patients were examined. The flow in the vertebral artery on the diseased side was reversed in three and normal in three.

#### *Angiography*

Four patients had been examined. Two had a subclavian occlusion and one a pronounced stenosis. In the latter patient the vertebral artery branched directly from the aorta. The fourth patient had an occlusion of the right subclavian artery, the flow direction in the vertebral artery could not be visualized. In the two patients with left subclavian occlusion the vertebral flow was reversed.

## DISCUSSION

In the present series comprising 25 patients with subclavian stenosis or occlusion, 18 had a reversed flow in the ipsilateral vertebral artery but only seven had neurological symptoms that may be ascribed to vertebrobasilar ischemia. Some patients with subclavian occlusive disease and a reversed vertebral flow were judged to have their symptoms not because of steal but because of associated carotid lesions. This is in accordance with the findings of Lord et al (14) that out of 42 patients with subclavian occlusive diseases and reversed flow in the vertebral artery, 15 had symptoms that could be ascribed to steal while 10 had symptomatic carotid insufficiency and 14 non specific neurological symptoms.

The high incidence of patients with subclavian occlusive disease without reversal of vertebral flow or without symptoms from a reversal of vertebral flow makes it desirable to examine the patients with non invasive methods before considering angiography.

Different techniques to assess the flow direction of the vertebral arteries by Doppler ultrasound have been described (8, 10, 13, 18). In patients with clinical signs of subclavian artery obliteration and neurological symptoms, the first measure should be to examine the vertebral blood flow direction by a non invasive method.

Subclavian artery obliteration relatively seldom causes arm claudication (12). Nine of our patients were referred to hospital on the suspicion that subclavian artery obliteration caused arm symptoms, but only in one patient was a reduced blood

capacity the limiting factor for arm working capacity. Thus in patients with arm symptoms a massive investigation of the arm circulation evaluation of blood flow and arm working capacity should be performed as the first measure.

## REFERENCES

1. K. & Bouke H. Die Infracoron-Oscilloskopie eine neue Methode zur Kontrolle der peripheren Durchblutung. *Klin Wochenschr* 31 1051 1953.
2. Sumner J M & Laurian C. Surgical management of vertebralbasilar insufficiency. *Cardiovasc Surg* 4 5 1976.
3. K. Plethysmographs usable during functional tests recording volume changes in ml per 100 ml of extremity. *Rep Steno Hosp* 6 147 1956.
4. Jorland A. A new vascular syndrome—"The subclavian steal". *N Engl J Med* 265 912 1961.
5. Ekström S. Continuous flow measurement during reconstruction of the carotid artery. *Scand J Thorac Cardiovasc Surg* 2 51 1968.
6. K. & Westersten A. Untersuchungen über Eigenschaften und Verwendungsmöglichkeiten eines neuen Extremitätenplethysmographen. *Acta Physiol Scand* 46 1 1959.
7. Mørksen J. Segmental measurements of systolic blood pressure in the extremities including the thumb and the great toe. *Acta Chir Scand (Suppl)* 426 1972.
8. Ze P & Zeuner H. Doppler sonographische Untersuchungen bei Subclavia Anzapfsyndrom. *Dtsch Med Wochenschr* 101 1912 1976.
9. Gier L. Limiting factors for aerobic muscle performance. *Acta Physiol Scand (Suppl)* 346 1970.
10. Keller H, Müller W, Meier W & Schönbeck M. Transorale Doppler Sonographie unter Schleimhautanästhesie zur Beurteilung der Stromungsverhältnisse in den Aa. vertebrales (Vertebral Doppler). *Dtsch Med Wochenschr* 100 943 1975.
11. Killen D A, Foster J H, Gobbel W G, Stephenson S E, Collins H A, Billings F T & Scott H W. The subclavian steal syndrome. *J Thorac Cardiovasc Surg* 51 539 1966.
12. Liljeqvist L, Ekström S & Nordhus O. Intrathoracic approach for subclavian and innominate artery reconstructions. *Scand J Thorac Cardiovasc Surg*. To be published.
13. —. Monitoring direction of vertebral blood flow by Doppler shift ultrasound in patients with suspected subclavian steal. Submitted to *Br J Surg*.
14. Lord R S A, Adair R & Stein R L. Contribution of the circle of Willis to the subclavian steal syndrome. *Circulation* 41 871 1969.
15. Magaard F & Rytman A. Regional cerebral blood flow and vertebral angiography at rest and in connection with arm work in patients with the subclavian steal phenomenon. *Scand J Thorac Cardiovasc Surg* 10 96 1976.
16. Marshall J. A survey of occlusive disease of the vertebralbasilar arterial system. In: *Handbook of clinical neurology* (ed P J Winken & G W Bruyn) vol 12 pp 1-12. North Holland Publishing Co, Amsterdam 1972.
17. Reivich M, Holling H E, Roberts B & Toole J F. Reversal of blood flow through the vertebral artery and its effect on cerebral circulation. *N Engl J Med* 265 868 1961.
18. Strandness D E & Sumner D S. Chapter 2. In: *Ultrasonic techniques in angiology* pp 54-55. Huber, Bern, Stuttgart and Vienna 1975.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97  
98  
99  
100  
101  
102  
103  
104  
105  
106  
107  
108  
109  
110  
111  
112  
113  
114  
115  
116  
117  
118  
119  
120  
121  
122  
123  
124  
125  
126  
127  
128  
129  
130  
131  
132  
133  
134  
135  
136  
137  
138  
139  
140  
141  
142  
143  
144  
145  
146  
147  
148  
149  
150  
151  
152  
153  
154  
155  
156  
157  
158  
159  
160  
161  
162  
163  
164  
165  
166  
167  
168  
169  
170  
171  
172  
173  
174  
175  
176  
177  
178  
179  
180  
181  
182  
183  
184  
185  
186  
187  
188  
189  
190  
191  
192  
193  
194  
195  
196  
197  
198  
199  
200  
201  
202  
203  
204  
205  
206  
207  
208  
209  
210  
211  
212  
213  
214  
215  
216  
217  
218  
219  
220  
221  
222  
223  
224  
225  
226  
227  
228  
229  
230  
231  
232  
233  
234  
235  
236  
237  
238  
239  
240  
241  
242  
243  
244  
245  
246  
247  
248  
249  
250  
251  
252  
253  
254  
255  
256  
257  
258  
259  
260  
261  
262  
263  
264  
265  
266  
267  
268  
269  
270  
271  
272  
273  
274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288  
289  
290  
291  
292  
293  
294  
295  
296  
297  
298  
299  
300  
301  
302  
303  
304  
305  
306  
307  
308  
309  
310  
311  
312  
313  
314  
315  
316  
317  
318  
319  
320  
321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335  
336  
337  
338  
339  
340  
341  
342  
343  
344  
345  
346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356  
357  
358  
359  
360  
361  
362  
363  
364  
365  
366  
367  
368  
369  
370  
371  
372  
373  
374  
375  
376  
377  
378  
379  
380  
381  
382  
383  
384  
385  
386  
387  
388  
389  
390  
391  
392  
393  
394  
395  
396  
397  
398  
399  
400  
401  
402  
403  
404  
405  
406  
407  
408  
409  
410  
411  
412  
413  
414  
415  
416  
417  
418  
419  
420  
421  
422  
423  
424  
425  
426  
427  
428  
429  
430  
431  
432  
433  
434  
435  
436  
437  
438  
439  
440  
441  
442  
443  
444  
445  
446  
447  
448  
449  
450  
451  
452  
453  
454  
455  
456  
457  
458  
459  
460  
461  
462  
463  
464  
465  
466  
467  
468  
469  
470  
471  
472  
473  
474  
475  
476  
477  
478  
479  
480  
481  
482  
483  
484  
485  
486  
487  
488  
489  
490  
491  
492  
493  
494  
495  
496  
497  
498  
499  
500  
501  
502  
503  
504  
505  
506  
507  
508  
509  
510  
511  
512  
513  
514  
515  
516  
517  
518  
519  
520  
521  
522  
523  
524  
525  
526  
527  
528  
529  
530  
531  
532  
533  
534  
535  
536  
537  
538  
539  
540  
541  
542  
543  
544  
545  
546  
547  
548  
549  
550  
551  
552  
553  
554  
555  
556  
557  
558  
559  
560  
561  
562  
563  
564  
565  
566  
567  
568  
569  
570  
571  
572  
573  
574  
575  
576  
577  
578  
579  
580  
581  
582  
583  
584  
585  
586  
587  
588  
589  
590  
591  
592  
593  
594  
595  
596  
597  
598  
599  
600  
601  
602  
603  
604  
605  
606  
607  
608  
609  
610  
611  
612  
613  
614  
615  
616  
617  
618  
619  
620  
621  
622  
623  
624  
625  
626  
627  
628  
629  
630  
631  
632  
633  
634  
635  
636  
637  
638  
639  
640  
641  
642  
643  
644  
645  
646  
647  
648  
649  
650  
651  
652  
653  
654  
655  
656  
657  
658  
659  
660  
661  
662  
663  
664  
665  
666  
667  
668  
669  
670  
671  
672  
673  
674  
675  
676  
677  
678  
679  
680  
681  
682  
683  
684  
685  
686  
687  
688  
689  
690  
691  
692  
693  
694  
695  
696  
697  
698  
699  
700  
701  
702  
703  
704  
705  
706  
707  
708  
709  
710  
711  
712  
713  
714  
715  
716  
717  
718  
719  
720  
721  
722  
723  
724  
725  
726  
727  
728  
729  
730  
731  
732  
733  
734  
735  
736  
737  
738  
739  
740  
741  
742  
743  
744  
745  
746  
747  
748  
749  
750  
751  
752  
753  
754  
755  
756  
757  
758  
759  
760  
761  
762  
763  
764  
765  
766  
767  
768  
769  
770  
771  
772  
773  
774  
775  
776  
777  
778  
779  
780  
781  
782  
783  
784  
785  
786  
787  
788  
789  
790  
791  
792  
793  
794  
795  
796  
797  
798  
799  
800  
801  
802  
803  
804  
805  
806  
807  
808  
809  
810  
811  
812  
813  
814  
815  
816  
817  
818  
819  
820  
821  
822  
823  
824  
825  
826  
827  
828  
829  
830  
831  
832  
833  
834  
835  
836  
837  
838  
839  
840  
84

51

e

1

 $t_0$ 

1

)

# Incidence and Significance of Heartmuscle Antibodies in Patients with Acute Myocardial Infarction and Unstable Angina

K L Liem J H ten Veen K I Lie T E W Feltkamp  
and D Durrer

*From the Departments of Cardiology and Clinical Physiology, Wilhelmina Gasthuis, Amsterdam, the Central Laboratory of the Netherlands Red Cross Blood Transfusion Service and the Laboratory for Experimental and Clinical Immunology of the University of Amsterdam, Amsterdam, The Netherlands*

**ACT** The incidence of heartmuscle anti- was studied prospectively in 136 patients newly admitted for acute myocardial infarction (AMI) and in 95 patients with unstable angina. Heartmuscle antibodies were determined with the immunofluorescence technique on days 1, 10, 30 in patients with AMI and on days 1 and 10 in patients with unstable angina. Heartmuscle antibodies were found in 16/136 AMI patients (12%) and in 13/95 (3%) with unstable angina. None of the patients developed post myocardial infarction syndrome in the 2-4 weeks after infarction or during 8-year follow up. The AMI patients with and without heartmuscle antibodies were comparable with respect to age, sex, site and size of infarction, incidence of early pericarditis and previous

coronary heart disease. Heartmuscle antibodies in patients with acute myocardial infarction and unstable angina.

Acta Med Scand 206 473 1979

complication following acute myocardial infarction (AMI) first described by Dressler (5) is known as the post myocardial infarction syndrome. This syndrome is characterized by the recurrence of chest pain and the presence of a pericardial friction rub in the 2nd-6th week after AMI, associated with leukocytosis, a rise in temperature and increase in ESR. In the following years Dressler described the condition in several publications and has presented a total of 44 cases. Mandel and Stein (17), Stein and Weinstein (18), Weiser et al., Broch and Ofstad (2) and Davidson et al. (4) reported identical cases during this period.

The incidence of this syndrome has been reported as about 3-4% of all cases of AMI (8). In a retrospective study Broch and Ofstad (2) found an incidence of about 1%.

The etiology of this syndrome is still unknown. Previously extension of myocardial infarction or pulmonary embolism have been regarded as possible causes (5). Later autoimmune reaction was considered as another causative mechanism since antibodies to cardiac tissue have been found in the serum of a considerable amount (23-55%) of these patients (8, 10, 11, 13, 14, 15, 19). However such antibodies have also been found in the absence of the syndrome (1, 10, 12, 16). Finally a viral etiology of the post myocardial infarction syndrome has been suggested (3, 15).

To evaluate the incidence of post myocardial infarction syndrome and the true significance of heartmuscle antibodies we have designed a prospective study in which heartmuscle antibodies were determined in patients with AMI. Heartmuscle antibodies were also determined in patients with unstable angina.

## PATIENTS AND METHODS

A number of 136 patients admitted consecutively to the Coronary Care Unit because of AMI and 95 because of unstable angina were studied prospectively. The diagnosis of AMI was based on a characteristic history of chest pain correlated with typical ECG changes and a serial rise in serum enzymes (LDH, CPK-MB and SGOT).

Infarct location was defined according to the criteria

**Abbreviations** AMI=acute myocardial infarction  
=antistreptolysin titre PBS=phosphate buffered

2

4

de

8  
vare  
15 (

der

el

1

11

6

12

1

This study revealed that heartmuscle antibodies present in a rather high percentage (12%) of patients in 3% of those with unstable angina and only 1% of 950 healthy blood donors. It is worthy that the two groups of AMI patients had without heartmuscle antibodies did not differ in the size of the infarct or the incidence of pericarditis.

From the above mentioned data and the absence of a typical post myocardial infarction syndrome suggest that heartmuscle antibodies cannot be considered as a specific and sensitive parameter for the subsequent development of a post myocardial infarction syndrome. However, these data showed that a relation may exist between the severity of symptomatic coronary artery disease and subsequent incidence of heartmuscle antibodies. Alternative explanations for the high incidence of heartmuscle antibodies might be evaluated by immunological studies.

#### ACKNOWLEDGEMENT

The authors are indebted to the Dutch Heart Foundation for the financial support of this study.

#### REFERENCES

1. Waters F J & Talano J V *Am Heart J* 1972
2. O J & Ofstad J *Acta Med Scand* 166 4
3. Burch G E & Colcolough H L *Am Heart J* 80 290 1970
4. Davidson C Oliver M F & Robertson R F *Br Med J* 2 5251 1961
5. Dressler W *Circulation* 12 697 1955
6. — *JAMA* 160 1379 1956
7. — *Heart Bull Pa Ed* 102 1958
8. — *Arch Intern Med* 103 28 1959
9. Dressler W Yurkofsky J & Starr M C *Am Heart J* 54 42 1957
10. Ehrenfeld E N Gery I & Davies A M *Lancet* 1 1138 1961
11. van der Geld H *Lancet* 2 617 1964
12. Golan D T & Kursbaum A *Clin Exp Immunol* 26 86 1976
13. Itoh K Ohkuni H Kimura E & Kimura Y *Jap Heart J* 10 485 1969
14. Kaplan M H & Frengley I D *Am J Cardiol* 24 459 1969
15. Kennedy H L & Das S K *Am Heart J* 91 233 1976
16. Kleinsorge H Dornbusch S & Romer R *Int Arch Allergy* 16 200 1960
17. Mandel W & Johnson E C *Am Heart J* 54 146 1957
18. Stein I & Weinstein J *Am Heart J* 54 146 1957
19. Strausz I & Dobias G Y *J Clin Pathol* 20 161 1967
20. The Criteria Committee of the New York Heart Association. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. Little Brown & Co. Boston 1973
21. Weiser N J Kantor M & Russell H K *Circulation* 20 371 1959
22. West M Eshchar J & Zimmerman H J *Med Clin North Amer* 50 171 1966



# Influence of a Myocardial Infarction on Blood Pressure and Serum Cholesterol

Michael McCall Dag Elmfeldt Anders Vedin Claes Wilhelmsson  
Hans Wedel and Lars Wilhelmsen

*From the Section of Preventive Cardiology Department of Medicine I Sahlgrenska Hospital  
Department of Medicine Östra Hospital Göteborg Sweden  
and Department of Medicine Perth Medical Centre Nedlands Australia*

**TRACT** Blood pressure (BP) was measured before and after acute myocardial infarction (MI) in 21 aged 49-60 years from a random population. Men on drugs affecting BP before MI or follow up were excluded. Pre- and postinfarction cholesterol levels were analyzed in 49 men not on lipidemic treatment recruited from the same random sample. The mean fall in systolic BP was 14 mmHg both five weeks and one year after the acute event, but 10 mmHg after two years. The fall in diastolic BP (DBP) was 10 mmHg five weeks after the MI and remained at this level for two years. The decreases in SBP and DBP were significant. There was a positive correlation between the fall in SGOT during the acute phase of MI and the decrease in DBP between preinfarction readings five weeks after the MI. Serum cholesterol was unchanged three months, and one year after the MI as compared to the preinfarction level.

**Index words:** blood pressure, serum cholesterol, myocardial infarction.  
*Scand J Clin Lab Invest* 206 477 1979

Hypertension and elevated serum cholesterol are well known risk factors for a first myocardial infarction (MI)—primary risk factors (18-25). These factors may also be of importance for predicting a second non-fatal MI—secondary risk factors (21). Numerous studies have shown hypertension to be a secondary risk factor (26) while the importance of the cholesterol level is probably less pronounced at least during the first years after MI (11) though some studies support its role as a secondary risk factor (20). Linear and non-linear combinations of levels of these and other risk factors have been used to calculate the risk of MI in non-symptomatic

subjects (24-25). In studies of post-MI patients it is sometimes of value to estimate the risk that the patient had run of getting his first MI before onset of symptoms based on the same risk factors. Calculations of this multivariate risk can be used to identify low risk subjects. In this category it is then possible to reveal other factors of importance for development of an MI (10). In order to execute the calculation it is necessary to estimate the level of the risk factors before the first MI from postinfarction values.

The purpose of this presentation is to report blood pressure (BP) and serum cholesterol levels before and after MI in a representative sample of middle-aged men.

## PATIENTS AND METHODS

The patients were all recruited from a multiple risk factor intervention trial which has been described elsewhere (24). Briefly the study group consists of all men living in Göteborg born between 1915 and 1922 and from 1924 to 1925. The subjects were initially randomly divided into three groups each comprising about 10 000 men. One group is the intervention group the other two serve as reference groups. The screening examination which began in 1970 was completed in 1973. Rescreening was performed four years after the initial screening and began in 1974. At screening the subjects' weight, total serum cholesterol and BP were recorded. The screening took place in the afternoon and the subjects were asked not to eat during four hours before the examination. BP was measured in the right arm according to WHO recommendations (17) after a five min interview in the sitting position. Diastolic BP (DBP) was recorded when the Korotkoff sounds disappeared (phase 5).

**Abbreviations:** MI=myocardial infarction, BP=blood pressure, SBP=systolic BP, DBP=diastolic BP.

Reprint requests to: L. Wilhelmsen, M.D., Department of Medicine, Östra Hospital, S-416 85 Go.



sible for the decrease in BP a similar decrease would be expected in cholesterol. This was not the case. Thus the present groups form their own group mean which again as such should not be subjected to regression to the mean.

Of necessity the present analysis has been mainly limited to patients not on hypotensive drugs before and after MI. Patients treated with such drugs before and/or after MI form a heterogeneous group. Due to modifications on account of the infarction the therapy given before is seldom identical to that prescribed postinfarction. And although a few patients did receive the same treatment before and after infarction the two conditions are not comparable because the mode of action of the drugs may differ and/or the patient's response may be changed. Therefore it would be difficult to interpret pre- and postinfarction comparisons in patients treated with hypotensive drugs. Nevertheless the group of patients who were treated did show the same reductions of SBP and DBP when they were analyzed separately. This supports the above conclusions that the present observations are not subjected to regression to the mean. Therefore the demonstrated reduction of 14/10 mmHg seems a reasonable estimation of the infarction induced BP reduction at five weeks and one year after the infarction. A flawless study on the influence of an MI on the BP of all patients in a series is difficult to conceive due to the necessity of treating post MI patients with e.g.  $\beta$  blockers or diuretics.

The significant relationships between fall in DBP and maximum SGOT while in hospital suggests that the former is at least partly a consequence of loss of heart muscle tissue. There are a number of studies relating the maximum SGOT level to the extent of damage in acute MI (5, 12, 21, 27). Other explanations are however not excluded. The slightly higher mean serum cholesterol in the men who subsequently suffered an MI compared with the population sample is expected because serum cholesterol is a major risk factor for MI. The difference shown is a minimum since subjects with considerably higher serum cholesterol values were treated with lipid lowering drugs and thus excluded from this study.

The mean cholesterol level three months after the MI did not differ significantly from the mean level at screening up to five years earlier nor did subsequent values one and two years after the MI change significantly. These findings which indicate that

the fall in serum cholesterol following MI is reversed within three months are in keeping with reports based on analyses during the acute phase follow up.

## ACKNOWLEDGEMENTS

Supported by grants from the Bank of Sweden Tercentenary Foundation and the Swedish National Association against Heart and Chest Diseases.

## REFERENCES

- 1 Armitage P, Fox W, Rose G A & Tinker P. The variability of measurement of casual blood pressure. II. Survey experience. *Clin Sci* 30: 337, 1966.
- 2 Armitage P & Rose G A. The variability of measurements of casual blood pressure. I. A laboratory study. *Clin Sci* 30: 325, 1966.
- 3 Astrup J, Bisgaard Frantzen H, Nielsen S & Sing N. Blood pressure lowering effect of myocardial infarction. *Lancet* 2: 903, 1976.
- 4 Bergstrand R, Wilhelmsson C, Vedin A & Helmsen, L. A population study of men 30-34 57-65 years of age. *Br J Prev Soc Med*. To be published.
- 5 Chapman B L. Relation of cardiac complications. SGOT level in acute myocardial infarction. *Br H* 34: 890, 1972.
- 6 Cotton S G. Plasma cholesterol after myocardial infarction. *Postgrad Med J* 46: 551, 1970.
- 7 Cramér K & Isaksson B. An evaluation of the Theorell method for the determination of total cholesterol. *Scand J Clin Lab Invest* 11: 713, 1959.
- 8 Elmfeldt D, Wilhelmsson L, Tibblin G, Vedin A, Wilhelmsson C & Bengtsson C. Registrations of myocardial infarction in the city of Göteborg—den—a community study. *J Chron Dis* 28: 173, 1975.
- 9 — A post myocardial infarction clinic in Göteborg—Sweden—a follow up of MI patients in a specialist patient clinic. *Acta Med Scand* 197: 497, 1974.
- 10 Elmfeldt D, Wilhelmsson L, Wedel H, Vedin A, Wilhelmsson C & Tibblin G. Primary risk factors in patients with myocardial infarction. *Am J* 91: 412, 1976.
- 11 Johansson S, Vedin A, Wilhelmsson C, Elmfeldt D & Wilhelmsson L. Prognostic cholesterol levels after myocardial infarction. *Heart J*. To be published.
- 12 Kåbe O & Nilsson N J. Observation on the prognostic and prognostic value of some enzymes in myocardial infarction. *Acta Med Scand* 181: 1967.
- 13 von Lohmann F W. Dissmann Th & Hypertonie und Myokardinfarkt unter besonderer Berücksichtigung des Blutdruckverhaltens. *Infarkt Z Kardiol* 63: 252, 1974.
- 14 Martin P J. The significance of serum cholesterol and triglyceride value in the post myocardial infarction period. *Clin Biochem* 8: 227, 1975.

- 21 Meyer H J Das Verhalten des Serum Cholesterins bei Herzinfarkt *Z Kreislaufforsch* 59 1970
- 22 Isaksson R Screening methods in community control of hypertension In *Pathophysiology and management of arterial hypertension* Sweden (ed G Berg and L Hansson & L Werko) p 250 Lundgren & Norstedt 1975
- 23 Gellera G & Blackburn H Cardiovascular survey methods WHO Geneva 1963
- 24 Goldberg D W The status of risk factors and coronary heart disease *J Chron Dis* 22 515 1970
- 25 Gellera J Atherosclerotic coronary heart disease: a major challenge to contemporary public health and preventive medicine *Conn Med* 28 675 1964
- 26 Coronary Drug Project. Factors influencing short-term prognosis after recovery from myocardial infarction—three year finding of the Coronary Drug Project *J Chron Dis* 27 267 1974
- 27 Tibblin G, Wilhelmsen L, Wedel H, Pettersson B, Wilhelmsen C, Elmfeldt D & Tibblin G Prediction of cardiovascular deaths and non fatal reinfarctions after myocardial infarction *Acta Med Scand* 201 309 1977
- 28 Welin G Om serumkolesterinet vid hjärtinfarkt *Nord Med* 37 324 1948
- 29 Wilhelmsen L, Bengtsson C, Elmfeldt D, Vedin A, Wilhelmsen C, Tibblin G, Lindquist O & Wedel H Multiple risk prediction of myocardial infarction in women as compared to men *Br Heart J* 39 1179 1977
- 30 Wilhelmsen L, Tibblin G & Werko L A primary preventive study in Gothenburg Sweden *Prev Med* 1 153 1972
- 31 Wilhelmsen L, Wedel H & Tibblin G Multivariate analysis of risk factors for coronary heart disease *Circulation* 48 950 1973
- 32 Wilhelmsen C, Vedin A, Elmfeldt D, Tibblin G & Wilhelmsen L Hypertension and myocardial infarction *J Chron Dis* 31 157 1978
- 33 Wroblewski F The clinical significance of transaminase activities of serum *Am J Med* 27 911 1959

11  
22  
33  
44  
55

66  
77  
88  
99  
100

11

22

33

44

55

# Myocardial Infarction Complicated by Heart Block— Treatment and Long-Term Prognosis

S Å Forsberg and S Juul Møller

*From the Medical Department Borås Hospital Borås  
and the University of Göteborg Göteborg Sweden*

A number of 597 patients with acute infarction (AMI) were treated with continuous monitoring of the heart rhythm in a coronary care unit for at least three days. We found 39 with heart block: 39 with complete, 29 with second degree and 16 with at most first degree heart block. The treatment was primarily conservative. 12 of the 39 patients with complete heart block were given isoproterenol and two received temporary pacemakers. Survival was traced over two years in the whole patient group with myocardial infarction. Heart block implied a worsened prognosis. In two years, but survival was independent of the degree of heart block. Among those with complete heart block, survival did not differ from comparable patient series from Copenhagen. Therefore all patients were given pacemakers. Temporary support of indiscriminate artificial pacemakers in patients with AMI and complete heart block results ought to be controlled in a randomized trial.

Myocardial infarction, heart block, treatment, prognosis.

Acta Med Scand 206 483-487 1979

Artificial cardiac pacemaker is of unquestionable value in chronic or intermittent complete heart block. It could therefore also seem logical to use temporary frequently transient heart block seen in myocardial infarction (AMI). Its positive long-term survival rates has, however, never been established and has even been questioned (4). Lack of documentation and our own experience led us to adopt a primarily conservative post-infarction pacemaker treatment in myocardial infarction. Although we do have the resources for this, the purpose was to study AMI patients treated in a coronary care unit (CCU) who developed heart

block, and the survival rate of these patients for a period of two years. Particular attention was paid to those with complete heart block.

## METHODS

The study population comprises all patients with a diagnosis of AMI admitted to the CCU at the Central Hospital in Borås during 1974 and 1975. The Medical Clinic cares for all patients with myocardial infarction among a population of approximately 130 000 residents. Patients with signs of a myocardial infarction were admitted to the CCU for at least three days. Patients with complicated infarction for longer periods. Subsequent care was given in the ordinary medical wards.

The diagnosis of cardiac infarction is based on stated criteria—symptoms, ECG findings, transaminase levels and autopsy findings. A standardized infarction record is used in the CCU.

The diagnosis of heart block is based on continuous monitoring of the ECG by oscilloscope and 12-lead ECG each morning for at least the first three days in the CCU. The patient group recorded as having heart block does not include those who displayed heart block only terminally or in direct association with electroconversion of ventricular fibrillation. The location of the infarction in patients with heart block was determined entirely from the ECG findings.

The treatment of all degrees of heart block was primarily expectant. In patients with syncope or bradycardia with hemodynamic complications, isoproterenol infusion was given in an effort to establish a heart rate of approximately 50–60/min. In patients who did not respond to therapy, a transvenous pacemaker was temporarily implanted. Patients with persistent complete heart block received permanent pacemakers.

The two-year survival rate in the entire study population has been investigated on the basis of information from hospital records and the central population register.

The patients were categorized in a manner somewhat similar to that used in a study by Leth et al. (6) from Copenhagen, which is the only one available for comparison.

Abbreviations: AMI, acute myocardial infarction; CCU, coronary care unit.

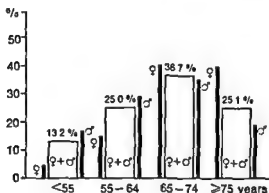


Fig 1 Age and sex distribution among 597 AMI patients

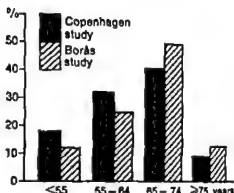


Fig 3 Age distribution among patients from Copenhagen (6) and Borås with AMI and complete heart block

son of the long term prognosis following cardiac infarction complicated by complete heart block. While we were restrictive with respect to pacing, all patients with complete heart block were paced in the Copenhagen study.

The variation of survival curves has been calculated according to Greenwood's estimate (1). Survival is presented in Fig 5 where the x-axis on the quadratic figure represents fractions of observation time and the y-axis represents fractions of the number of patients observed. The area under the survival curves was calculated and expressed as a fraction of the total surface of the square. This figure represents the fractional life time  $F_L$ , i.e. survival as a fraction of the total observation time.  $F_D = (1 - F_L)$  is the time of being dead as a fraction of the total observation time.

## PATIENTS

During the observation period, the diagnosis of AMI was made in 602 patients treated in the CCU. Five patients could not be traced for the two-year period and were therefore excluded. 597 patients were thus left for the study. Age and sex distribution is shown in Fig 1.

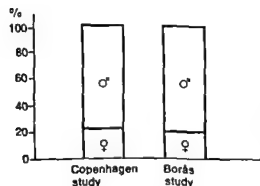


Fig 2 Sex distribution among 56 patients from Copenhagen (6) and 39 from Borås with AMI and complete heart block

## RESULTS

Of the 597 patients, 85 had heart block—40 in 1st degree, 40 at most second degree in 29 at most third degree in 16, corresponding to incidences of 6.7 and 2.7%, or roughly 7.5 and 3%. One patient admitted twice with cardiac infarction complicated by temporary complete heart block, but the first infarct is included in the subsequent analysis.

Sex and age distribution among the 39 patients with complete heart block and the location of the infarctions are shown in Figs 2, 3 and 4. Survival curves for the entire infarct population and those with heart block are given in Fig 5 and different degrees of heart block in Fig 6. Of the infarctions with heart block, 16 (41%) were anterior, 16 (41%) were posterior, and 7 (18%) were of unknown location. There is no significant difference between this figure and that for patients without heart block.

Fig 5 shows that at every interval over the

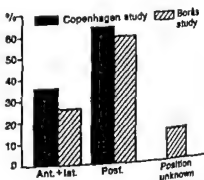


Fig 4 Location of infarctions with complete heart block in patients from Copenhagen (6) and Borås (39). A does not exclude an additional posterior infarction

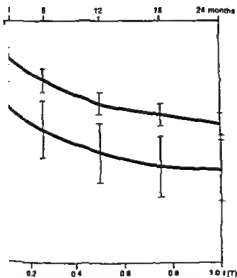


Fig 6 Survival during two years after AMI among 597 (upper curve) and among those who also had heart block (lower curve). Two standard deviations are indicated.

and the patients with heart block had a notably lower survival than all the patients in the Copenhagen population. Fig 6 shows that the survival was not related to the degree of heart block. In our study, patients with complete heart block compared our results with those of the Copenhagen study (6). Fig 4 shows the location of

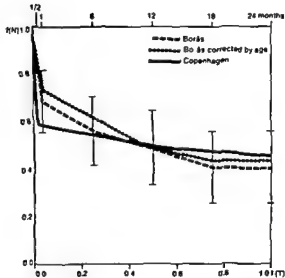


Fig 7 Survival among 39 patients from Borås with two standard deviations indicated and 56 from Copenhagen (6) with AMI and complete heart block. Included is also the patient group from Borås corrected by age to the Copenhagen study.

infarctions in the two studies. Among the six cases with position unknown, autopsy was performed in three and disclosed two with anterior and one with only posterior infarction. Considering the few unclassified patients in our series, it can be said that the proportion of patients with infarction at the various locations is approximately the same in the two studies. Our patients were somewhat older, and for this reason we have calculated the average mortality for each age group. Using these figures, a new study group was constructed with the same age distribution as in the Copenhagen study.

Fig 7 shows survival rates over the two year period for the two groups compared together with the corresponding curve for our uncorrected study group. The two week survival among the patients from Copenhagen is assumed to correspond to what that report terms hospital mortality. Despite the differences in therapeutic principles, there is no significant difference in survival between any of the three groups as observed at 1, 12 and 24 months. The fractional life time in our uncorrected group is 0.51, in our corrected group 0.53, and in the Copenhagen group 0.52. In accordance with our standard therapeutic procedure, temporary pace makers were implanted in two patients and a permanent pacemaker in another patient in the postacute phase following persistent CO

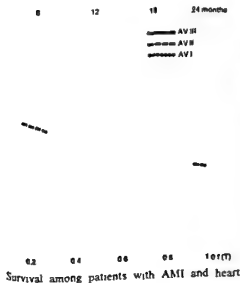


Fig 8 Survival among patients with AMI and heart block, categorized by degree of heart block (AVI, AVB, AVN).

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
61  
62  
63  
64  
65  
66  
67  
68  
69  
70  
71  
72  
73  
74  
75  
76  
77  
78  
79  
80  
81  
82  
83  
84  
85  
86  
87  
88  
89  
90  
91  
92  
93  
94  
95  
96  
97  
98  
99  
100

# Central and Renal Circulation, Renin and Aldosterone in Plasma during Prazosin Treatment in Essential Hypertension

D. K. Falch, A. Quist Paulsen, A. E. Ødegaard and N. Norman

From the Hormone and Isotope Laboratory, Aker Hospital, Oslo, Norway

**ABSTRACT** The hemodynamic adaptation and the renin-aldosterone system during treatment with a new vasodilating drug, prazosin (1), were studied in 14 patients with essential hypertension before and after 2 and 4 months of treatment. The mean daily dose was 2 mg/day for the first 2 months and was increased individually up to 4 mg/day during the last 2 months. In those patients treated for 2 months, the mean arterial blood pressure (MAP) remained unchanged. The reduction of MAP was mainly due to a decrease in peripheral resistance, but also to a decrease in cardiac output in 4 of the patients. Effective renal plasma flow increased from 220 to 254 ml/min  $m^2$ , whereas as a result of a fall in vascular resistance in the peripheral vessels. The plasma volume showed a small increase after 2 months, from 19.0 to 20.0 l, whereas pulmonary plasma volume was unchanged, indicating a slight redistribution of plasma between the pulmonary and the systemic circulation. Body weight increased from 75.1 to 76.1 kg, although a crude parameter might indicate volume expansion. Plasma renin activity increased a small, transient increase after 2 months from 4.6 to 6.5 nmol  $A_1/l$  h, whereas plasma aldosterone concentration was unchanged, indicating that volume expansion was not a result of a stimulation of the renin-aldosterone system. The serum sodium and chloride concentrations fell from 142.7 to 140.2 mmol/l and from 105.9 to 103.1 mmol/l, respectively.

**Key words:** hypertension, heart, cardiovascular system, vessels, kidney, blood volume, renin.

Acta Med Scand 206 489-1979

Prazosin is a relatively new antihypertensive drug which elicits vasodilation in both the arterial and venous segments of the systemic circulation (1). The resulting reduction in peripheral resistance is the basis for its use in essential hypertension (1, 7, 23, 24, 30). Reflex tachycardia and increased cardiac output, which are often seen during treat-

ment with other vasodilating drugs such as hydralazine (6, 12, 25, 33), are essentially absent during prazosin administration (25).

Messerli et al. (27) studying untreated cases with borderline hypertension observed a positive correlation between cardiac output and cardiopulmonary blood volume, and an inverse correlation between peripheral resistance and blood volume. An increase in the systemic intravascular volume resulting from arteriolar and venous dilatation by prazosin might lead to a redistribution of blood between the pulmonary and the systemic circulation. Furthermore, a generalized arteriolar dilatation might lead to an increase in renal blood flow in spite of unchanged cardiac output and a fall in blood pressure. The changes in circulatory pattern, pressure and intravascular volume might also influence the renin-aldosterone system (9, 10).

The aim of the present investigation was to study the hemodynamic adaptation and the change in the renin-aldosterone system during prazosin treatment in order to obtain a better understanding of the action of the drug when applied in the treatment of essential hypertension.

## PATIENTS

Fourteen patients, five females and nine males, 37-65 years of age (mean 49.3) were included. They were informed volunteers with essential hypertension, stage I or II according to the WHO classification. The diagnosis was based on clinical examination, blood and urine

**Abbreviations:** BP=blood pressure, MAP=mean arterial blood pressure,  $[^{125}I]$ OHI= $[^{125}I]$  orthoiodohippuran, ERPF=effective renal plasma flow, CI=cardiac index,  $CI_{pul}=C_{pul}$  plasma flow, IVCT=interventricular circulation time, pulmonary circulation time, PPV=pulmonary volume, LVWI=left ventricular work index,  $PR_{pul}$ =peripheral resistance index.



Table 1 Hemodynamic variables estimated at a 2 month interval in ten untreated patients with essential hypertension

C=control 2 M=2 months later

		Mean	S E M
ERPF (ml/min m <sup>2</sup> )	C	257	15
	2M	238	29
Body weight (kg)	C	76.7	3.6
	2M	76.8	3.5
Plasma volume (ml/cm)	C	19.0	0.6
	2M	18.8	0.7
Blood volume (ml/cm)	C	31.0	0.9
	2M	30.5	1.2
PPV (ml/m <sup>2</sup> )	C	178	8
	2M	173	8
IVCT (s)	C	7.08	0.36
	2M	7.36	0.46
CI (l/min m <sup>2</sup> )	C	3.796	0.192
	2M	3.527	0.220
Heart rate (beats/min)	C	67.2	2.9
	2M	64.4	3.1
MAP (mmHg)	C	114	2
	2M	115	3
LVW1 (W/m <sup>2</sup> )	C	0.93	0.05
	2M	0.89	0.07
TPRI (10 <sup>3</sup> N s m <sup>-2</sup> )	C	2.450	127
	2M	2.678	134
Plasma renin activity (nmol A <sub>1</sub> /l h)	C	0.19	0.04
	2M	0.14	0.02
Plasma aldosterone (pmol/l)	C	190	17
	2M	165	19
Serum sodium (mmol/l)	C	140.7	1.0
	2M	140.0	1.5
Serum potassium (nmol/l)	C	3.96	0.12
	2M	4.13	0.12
Serum chloride (mmol/l)	C	104	1.3
	2M	106.1	0.7
urea (l/l)	C	5.42	0.36
	2M	5.77	0.49

0.5 for all variables

analyses ECG chest X ray renography and determination of plasma renin activity and plasma aldosterone concentration before and after stimulation with furosemide in some cases urography was also performed.

The reference values (mean  $\pm$  S.D.) were body height 172.7  $\pm$  12.4 cm body weight 75.2  $\pm$  14.5 kg systolic BP (sitting position) 179  $\pm$  26 mmHg diastolic BP 113  $\pm$  10 mmHg cardiac volume (X ray) 425  $\pm$  62 ml/m<sup>2</sup> blood urea 5.1  $\pm$  1.4 mmol/l serum creatinine 85.8  $\pm$  25.9  $\mu$ mol/l.

Four patients had taken antihypertensive drugs previously (alprenolol trichlormethiazide methyldopa or chlorthalidone). These drugs were withdrawn at least 4 weeks before the start of the study. Three additional

patients had to be excluded after a few weeks of treatment two due to technical errors and one because of intolerance. Two of the females were menstruating. They were both studied in their follicular phases (37).

## METHODS

The patients were studied before and after 2 and 4 months of treatment with prazosin (Peripress® Pfizer). They were ambulatory and examined on an out patient basis. They were received in the laboratory at 8 a.m. after a breakfast and no previous exercise. The measurements were started after 60 min rest in the supine position. The control measurements (see below) the patients were given prazosin. The daily dose was gradually increased from 0.5 mg in the first evening to 0.5 mg twice during the first week and 1 mg twice daily thereafter. During the first 2 months of treatment clinical examinations were performed every 2nd week. Six of the patients still had an elevated mean arterial BP (MAP) 115 mmHg after 2 months of treatment. The daily doses were increased individually up to 3.5 mg twice during the last 2 months of the study (BP control 2nd week). On days of study the drug was taken 2 hours before the start of measurements.

## Renography

The individual kidney [<sup>125</sup>I] orthiodiodipyranoate clearance effective renal plasma flow (ERPF) was determined with a quantitative renographic technique described previously (28, 29). The basis for the ERPF calculation was the net kidney uptake of [<sup>125</sup>I] OIH 12-14 after a bolus injection.

## Cardiography

Cardiac output was estimated with a radiocardiographic technique employing a gamma camera. A Cine 700 of the technique for rapid sequential uptake and data handling with <sup>113m</sup>indium transferrin as the intravascular label as previously described (11, 12, 13, 14). Blood and plasma samples were drawn 10, 20 and 30 min after the bolus injection of <sup>113m</sup>indium. The specific activity of the tracer in the samples allowed for calculation of tracer contents at the time of injection.

The arterial BP was measured automatically on the arm with an Arteriosonde (Roche).

The radiocardiographic parameters were calculated previously described (11). The blood and plasma volumes were calculated from the dose of <sup>113m</sup>In given the specific activity in blood and plasma being corrected to bolus injection time. Cardiac index (CI) of plasma (CI<sub>p</sub> ml/min m<sup>2</sup>) was calculated from CI of blood as CI<sub>p</sub> = CI<sub>b</sub> / C<sub>b</sub> where C<sub>b</sub> is the radioactivity of <sup>113m</sup>In expressed in ml of the whole blood and C<sub>p</sub> the corresponding specific activity expressed in cpm/ml of plasma at bolus injection time. The interventricular circulation time (IVCT) plasma was determined as the time between the peaks of the dilution curves generated for the right and left ventricles.

Mean pulmonary circulation time (PCT) was calculated as 70% of IVCT. Pulmonary plasma volume (PPV) was calculated by multiplying the CI<sub>p</sub>s by PCT.

Table II Changes from the control study (C) to estimations 2 (2M) and 4 (4M) months after prazosin treatment (n=14)

		Mean	S.E.M.	p
volume (ml/cm)	C	19.0	1.0	
	2M	20.0	0.8	0.05
	4M	19.8	0.7	NS
L.VW <sup>2</sup>	C	163	9	
	2M	172	11	NS
	4M	171	11	NS
P <sub>1</sub>	C	7.03	0.58	
	2M	7.37	0.50	NS
	4M	7.31	0.39	NS
weight (kg)	C	75.1	3.8	
	2M	75.8	4.0	<0.05
	4M	77.1	4.0	<0.05
renin activity (nmol A <sub>2</sub> /l h)	C	0.46	0.11	
	2M	0.65	0.11	<0.05
	4M	0.42	0.12	NS
aldosterone (pmol/l)	C	241	31	
	2M	274	25	NS
	4M	290	40	NS

NS, not significant.

was calculated from systolic (SAP) and diastolic pressure as  $(SAP+2 \text{ DAP})/3$  (mmHg). Left atrial work index (L.VWI) and total peripheral resistance (TPR) were calculated as follows:  $L.VWI = \frac{P_{10} \times Q}{n \times m^2}$ ,  $MAP$  (mmHg)  $13.6 \text{ g/cm}^2 \times 1/1000$ ,  $0.16$  [TPR] =  $MAP$  (mmHg)  $80/CI$  (l/min  $m^2$ ) ( $10^3$  dyn  $s \text{ cm}^{-5} m^2$ ) where 13.6 is the specific gravity of Hg, 0.16 a converting factor from  $kpm/min$  (W) and 80 a converting factor from  $mmHg/l$  (dyn  $s \text{ cm}^{-5}$ ).

#### Reproducibility

The coefficient of correlation for ERPF estimated simultaneously with constant infusion technique and the renographic technique in 71 patients was 0.93 (28). Similarly, the coefficient of correlation for cardiac output measured by dilution technique based on continuous measurement of arterial blood and the cardiographic technique in 38 patients was 0.96 (11). The coefficient of variation calculated on the basis of measurements performed with the renographic technique at a 30-min interval in 18 patients with essential hypertension was for plasma volume 7.4%, L.VWI 10.7% and PPV 11.7%. The coefficient of variation for ERPF was 12.5% calculated on duplicate measurements in 38 patients with essential hypertension.

There were no statistically significant changes in the parameters estimated at a 2-month interval in ten untreated (four males, six females, aged 31–57 years) with hypertension stage I or II as illustrated in Table II. The systolic and diastolic blood pressures (mean  $\pm$  S.D.) were  $106 \pm 10$  mmHg respectively. The renin activity and plasma aldosterone were  $0.46 \pm 0.11$  nmol A<sub>2</sub>/l h and  $241 \pm 31$  pmol/l respectively. Their coefficients

of variation were 6.9% and 5% respectively. Blood urea, serum creatinine and serum electrolytes were determined with a Technicon SMA 12/60 Autoanalyzer (Central Laboratory, Aker Hospital).

The observed values after 2 and 4 months were compared with the control values using Student's *t* test for paired observations.

## RESULTS

As can be seen from Table I, no statistical changes occurred in the variables when estimated at two-month intervals in 10 untreated hypertensive patients.

Almost all patients in the treatment group reported slight sedation during the first weeks of treatment. Two of them also had a tendency to orthostatic dizziness. Some of the patients complained of headache and palpitations. The patients were informed of possible side effects of the drug before the start of treatment, and all but one volunteered to continue on the prescribed dose despite initial complaints. Most side effects disappeared after a couple of weeks. Prazosin was withdrawn in one patient because of impotence which disappeared after cessation of the drug. As shown in Table II, there was a slight increase in total plasma volume, barely statistically significant after 4 months of treatment. There was a slight decrease in the mean PPV, but the change was not

Table III Changes in kidney function variables and serum electrolytes from the control study (C) to estimations 2 (2M) and 4 (4M) months after prazosin treatment (n=14)

		Mean	S E M	p
ERPF (ml/min m <sup>2</sup> )	C	220	13	
	2M	252	13	NS
	4M	254	12	<0.05
Blood urea nitrogen (mmol/l)	C	5.1	0.4	
	2M	5.4	0.4	NS
	4M	5.3	0.3	NS
Serum creatinine (μmol/l)	C	85.5	7.0	
	2M	88.9	6.9	NS
	4M	90.7	4.6	NS
Serum sodium (mmol/l)	C	142.7	0.9	
	2M	141.0	0.7	NS
	4M	140.2	0.7	<0.02
Serum potassium (nmol/l)	C	4.1	0.1	
	2M	4.0	0.1	NS
	4M	4.0	0.1	NS
Serum chloride (mmol/l)	C	105.9	0.6	
	2M	104.9	0.5	NS
	4M	103.1	0.8	<0.02

NS=p&gt;0.05

significant. Neither was there any statistically significant change in the IVCT for plasma. Plasma renin activity increased slightly after two months of treatment but fell to pretreatment levels after four months. The mean value of plasma aldosterone increased but the change was not statistically significant.

Table IV Changes in systemic hemodynamic variables from the control study (C) to estimations 2 (2M) and 4 (4M) months after prazosin treatment (n=14)

		Mean	S E M	p
MAP (mmHg)	C	132.2	4.8	
	2M	123.0	3.9	<0.01
	4M	118.7	4.6	<0.01
CO (l/min m <sup>2</sup> )	C	3.47	0.21	
	2M	3.47	0.21	NS
	4M	3.42	0.14	NS
Heart rate (beats/min)	C	71.0	3.6	
	2M	68.1	4.7	NS
	4M	65.4	2.5	<0.01
Stroke index (ml/beat)	C	50	3	
	2M	52	3	NS
	4M	53	2	NS
TPRI (10 <sup>3</sup> N s m <sup>-2</sup> )	C	3.187	189	
	2M	2.956	169	NS
	4M	2.844	168	<0.05

NS=p&gt;0.05

Body weight was increased after 2 and 4 months of treatment.

As evident from Table III, ERPF showed a slight increase after 4 months of treatment while blood urea and serum creatinine were unchanged. Serum sodium and chloride both displayed a slight but statistically significant decline after 4 months of treatment.

The changes in the systemic hemodynamic variables are given in Table IV. MAP fell in 13 of 14 patients. The fall was mainly due to a decrease in peripheral resistance. In 4 of the patients however, the reduction of MAP was due to a fall in cardiac output. There was a statistically significant increase in heart rate and a slight but non significant increase in stroke volume.

## DISCUSSION

The observed changes in the measured variables during prazosin treatment are small. The ability of the methods to detect small changes in the variables is important in the evaluation of the results. The coefficients of variation as estimated from duplicate determinations (see Methods) suggest that the errors and reproducibility of the methods are within an acceptable range. The lack of statistical

in the measured variables estimated at a 2 h interval in ten untreated hypertensives (Table 1) adds to the validation of the changes observed in the treatment group.

Almost all patients noticed side effects during the first days of treatment. Side effects like headache, dizziness and palpitations are well known (1, 2, 4, 15, 17). Impotence however is noticed more seldom.

There was a slight increase in total plasma volume after 2 months of treatment whereas PPV was unchanged. This might indicate a small transient increase in intravascular volume predominantly in the systemic circulation. It must however be remembered that PPV is the product of cardiac output and plasma and PCT (11) and includes the errors of these measurements. The circulation time in plasma was however unchanged which indicates that the pulmonary intravascular volume was unchanged (11).

The increased plasma volume during prazosin administration which has also been observed by others (18) and Koshy et al (20) taken together with the increased body weight might indicate water and sodium retention even if changes in body weight constitute a crude parameter of changes in extracellular volume. Volume expansion has been observed during treatment with other vasodilators such as hydralazine (19). Furthermore the rate fall in serum sodium and serum chloride concentrations could indicate a certain amount of fluid dilution. Masoni et al (24) also found a tendency for serum sodium to decline in 5 patients treated during prazosin treatment. The reason for this is unknown but Maxwell (26) observed a fall in renal clearance in 4 hypertensives treated with prazosin.

Vasodilators such as dihydralazine elicit a considerable increase in plasma renin activity (12) probably because of secondary sympathetic stimulation. In the present study there was only a transient increase after 2 months of treatment. Hayes et al (16, 17) observed a fall in plasma renin activity during prazosin administration. The explanation probably is that prazosin elicits a sympatholytic effect and also a tendency to volume expansion which is in agreement with the unchanged plasma aldosterone concentration.

Reports concerning the effect of prazosin on renal circulation are scanty. Koshy et al (20) found no change in paraaminohippuric acid clearance (6 pa-

tients) after 8 weeks of prazosin treatment. Maxwell (26) estimated ERPF in 4 hypertensives and found a decrease in 2 and no change in the other 2 whereas Masoni et al (24) observed an increase in 5 subjects studied. In the present study there was a statistically significant increase in ERPF after 4 months of treatment a rise being noted in 11 of the 14 patients. This increment to the clearance of [ $^{131}$ I] OIH most likely is due to an increase in renal blood flow as a result of a fall in renal vascular resistance indicating an interference with the hemodynamic autoregulation in the kidneys. This may be an important effect since renal plasma flow is reduced in patients with essential hypertension (3, 5) and a further reduction has been observed during treatment with an antihypertensive drug such as propranolol (13). Blood urea and serum creatinine were unchanged. This precludes gross changes in glomerular filtration rate in accordance with reports by Ibsen et al (18), Bailey (2), Curtis and Bateman (8), Maxwell (26) and Koshy et al (20).

MAP fell in all the patients due to declines in both systolic and diastolic BP. This fall was mainly due to a decrease in peripheral resistance which is in agreement with previous reports (1, 7, 22, 23, 24, 30) but in 4 patients it reflected a decrease in cardiac output. The fall in heart rate supports the concept that prazosin elicits a sympatholytic effect (7) in contrast to the reflex tachycardia observed during hydralazine administration (12, 33).

From the present data it can be concluded that prazosin in small doses induced favourable hemodynamic changes through a fall in BP mainly reflecting a fall in peripheral resistance, a reduction in heart rate, an increase in renal plasma flow and no increase in plasma aldosterone concentration. The transient increase in plasma renin activity was small. The transient slight increase in systemic intravascular volume and the weight gain might indicate fluid retention which was not a result of stimulation of the renin-aldosterone system. There was no increase in PPV indicating a small redistribution of plasma between the pulmonary and the systemic circulation. A decline in serum sodium and chloride was also observed.

#### ACKNOWLEDGEMENTS

This work has been supported by grants from the Norwegian Medical Depot and Gimsøy legatet.

## REFERENCES

- 1 Awan N A, Miles R R, Maxwell K & Mason D T. Effects of prazosin on forearm resistance and capacitance vessels. *Clin Pharmacol Ther* 22: 79, 1977.
- 2 Bailey R R. Prazosin in the treatment of patients with hypertension and renal functional impairment. *Med J Aust (Spec Suppl)* 2: 42, 1977.
- 3 Baldwin D S, Hulet W H, Biggs A W, Gombos E A & Chasis H. Renal function in the separate kidney in man. II. Hemodynamics and excretion of solute and water in essential hypertension. *J Clin Invest* 39: 395, 1960.
- 4 Bolli P & Simpson F O. A preliminary clinical trial of prazosin. A new oral antihypertensive agent. *NZ Med J* 79: 969, 1974.
- 5 Chasis H & Redisch J. Effective renal blood flow in the separate kidneys of subjects with essential hypertension. *J Clin Invest* 20: 655, 1941.
- 6 Chatterjee K, Parmley W W, Massie B, Greenberg B, Berner J, Klausner S & Norman A. Oral hydralazine therapy for chronic refractory heart failure. *Circulation* 54: 879, 1976.
- 7 Constantine J W, McShane W K, Scwabine D & Hess H J. Analysis of the hypotensive action of prazosin. In: *Mechanisms and management* (ed. G. Onesti, K. E. Kim and J. H. Mayer) p. 429. Grune & Stratton, New York, 1973.
- 8 Curtis J R & Bateman F J A. Use of prazosin in management of hypertension in patients with chronic renal failure and in renal transplant recipients. *Br Med J* 4: 432, 1975.
- 9 Davis J O & Freeman R H. Mechanisms regulating renin release. *Physiol Rev* 56: 1, 1976.
- 10 Eide I, Løyning E & Kull F. Evidence for hemodynamic autoregulation of renin release. *Circ Res* 32: 237, 1973.
- 11 Falch D K & Norman N. Evaluation of a computerized technique for determination of cardiac output and central circulation times using gamma camera and  $^{113m}$ indium. *Scand J Clin Lab Invest* 34: 207, 1974.
- 12 —. The cardiac response to a small i.v. dose of dihydralazine: a safe drug for diagnostic tests? *Acta Med Scand* 203: 433, 1978.
- 13 Falch D K, Ødegaard A E & Norman N. Renal flow and cardiac output during hydralazine treatment in essential hypertension. *J Clin Lab Invest* 38: 143, 1978.
- 14 Falch D K & Strømme S B. Pulmonary plasma flow in relation to total plasma volume and intravascular circulation time in physically trained and untrained subjects. *Eur J Appl Physiol* 40: 211, 1979.
- 15 Graham R M, Thornell I R & Gain J M. Prazosin: The first-dose phenomenon. *Br Med J* 2: 1293, 1976.
- 16 Hayes J M. Prazosin in severe hypertension. Effect on blood pressure, plasma renin activity and in hypertensive emergencies. *Med J Aust (Spec Suppl)* 2: 30, 1977.
- 17 Hayes J M, Graham R M, O'Connell B P, Muir M R, Speers E & Humphrey T J. Experience with prazosin in the treatment of patients with severe hypertension. *Med J Aust* 1: 562, 1976.
- 18 Ibsen H, Rasmussen K & Erenlund H. Changes in plasma volume, extracellular fluid volume, glomerular filtration rate during combined treatment with propranolol and prazosin in hypertensive patients. *Curr Med Res Opin (Suppl)* 4: 83, 1977.
- 19 Ibsen H, Rasmussen K, Erenlund H, Jensen I, Leith A. Changes in plasma volume and extracellular fluid volume after addition of hydralazine to propranolol treatment in patients with hypertension. *Med Scand* 203: 419, 1978.
- 20 Koshy M C, Mickley D, Bourgoignie J, Flaufox D. Physiologic evaluation of a new hypertensive agent: prazosin. *Helv Circulation* 55: 1977.
- 21 Löwenstein J & Steele J M Jr. Prazosin. *Heart J* 95: 262, 1978.
- 22 Lund Johansen P. Prazosin. Evaluation of a new antihypertensive agent. *Excerpta Med ICS* 331: 1974.
- 23 —. Hemodynamic long term effects of prazosin and tolamolol in essential hypertension. *Br J Clin Pharmacol* 4: 141, 1977.
- 24 Masoni A, Tommasi A M, Baggioni F & Baggiolini P. Hemodynamic study in men of medium term treatment with a new amino-quinazoline antihypertensive agent (prazosin). *Excerpta Med ICS* 331: 54, 1974.
- 25 Massingham R & Hauen M L. A comparison of the effects of prazosin and hydralazine in blood pressure, heart rate and plasma renin activity in renal hypertensive dogs. *Eur J Pharmacol* 30: 1973.
- 26 Maxwell M H. Effects of prazosin on renal function and fluid electrolyte metabolism. *Postgrad Med J* 36: 41, 1974.
- 27 Messerli F H, De Carvalho J G R, Christensen & Frohlich E D. Systemic and regional hemodynamics in low normal and high cardiac output borderline hypertension. *Circulation* 58: 441, 1978.
- 28 Norman N. Effective plasma flow of the individual kidney. Determination on the basis of the  $^{113m}$ indium renogram. *Scand J Clin Lab Invest* 30: 395, 1970.
- 29 Norman N, Sundsfjord J A & Sturis J. Effective renal plasma flow (ERPF) of the individual kidney, renal venous renin activity (RVRA) determined simultaneously before and after the administration of hydralazine in renovascular hypertension. *J Clin Lab Invest* 35: 219, 1975.
- 30 Onesti G, Fernandes M A, Kim K E & C. D. Prazosin in the treatment of hypertension. *J Pharmacol Ther* 15: 216, 1974.
- 31 Sundsfjord J A. Radioimmunological determination of plasma renin activity during menstrual cycle during acute progesterone administration. *Acta endocrinol (Kbh)* 67: 174, 1971.
- 32 Sundsfjord J A & Aakvaag A. Variations in plasma aldosterone and plasma renin activity during the menstrual cycle: special reference to the ovulatory period. *Acta Endocrinol (Kbh)* 73: 499, 1971.
- 33 Wilkinson E L, Beckman H & Hecht H. Cardiovascular and renal adjustments to a diuretic agent (1-hydrazinophthalazine, CIBA BA aprezoline). *J Clin Invest* 31: 872, 1952.

## Malignant Hypertension— Improving Prognosis in a Rare Disease

T Gudbrandsson L Hansson H Herlitz and L Andren

*From the Departments of Internal Medicine Östra Hospital and Sahlgren's Hospital  
University of Göteborg Göteborg Sweden*

**ABSTRACT** A follow up was made of 69 patients regarded as having malignant hypertension during 5 years. Essential in 26, secondary in 39 and unclassified in 4. A clear male dominance was seen (41 men, 28 women), particularly in the group with essential hypertension (18 men, 8 women). The mortality in this study was less than in previously published studies. Thus, the 5 year survival rate was 75% in those with essential and 72% in those with secondary hypertension. In part this was due to haemodialysis and renal transplantation. The importance of renal function at the time of diagnosis was shown in this study. In most patients with essential hypertension and serum creatinine levels below 300 µmol/l renal function could be maintained or improved when antihypertensive treatment was instituted. Whereas progression of the renal damage was observed in those with serum creatinine levels above 300 µmol/l in spite of antihypertensive treatment with 3 drugs. The incidence of new cases of malignant hypertension tended to decrease during the observation period, particularly as regards essential hypertension.

**Key words:** malignant hypertension, prognosis, survival, symptoms, renal function.

Acta Med Scand 206 495-499 1979

Malignant hypertension is a serious condition. Its characteristics were defined already in 1914. They included severe hypertension, retinopathy with papilloedema, impairment of renal function, fibrinoid necrosis in the kidneys and a progressive and fatal clinical course. Keith (8) demonstrated in 1939 that the average survival time for untreated patients with degree III retinopathy was only 10.5 months. There was only no 5 year survival in this group. When antihypertensive treatment became possible in the early 1950s a significant reduction in mortality

occurred (4-13). The progress to uraemia could be halted at least in patients who at the time of diagnosis had close to normal renal function. A further improvement of the survival rate in malignant hypertension probably due to the availability of new and improved antihypertensive agents was achieved in the 1960s. Thus 50-60% 5 year survival was demonstrated (7). During the last decade a few studies have shown that even in patients with initially severely impaired renal function a return towards more normal levels of renal function can be obtained, probably as an effect of aggressive antihypertensive treatment (9-11).

The incidence of malignant hypertension is very low in screening examinations of various populations. In hospital series, however, a certain percentage of patients admitted with hypertension can still be classified as having malignant hypertension (6).

The purpose of this investigation was to follow up all registered cases of malignant hypertension at a large medical centre in Sweden during the years 1969-76 and to evaluate the prognosis and prognostic factors, mainly renal function, as well as the annual incidence of new cases of malignant hypertension.

### PATIENTS AND METHODS

All registered cases of malignant hypertension, fundoscopic changes of degree III or IV (Keith-Wagener and Barker classification) (8) at Sahlgren's University Hospital in Göteborg, Sweden, during an 8 year period (1969-76) were studied. All grade III patients had both exudates and haemorrhages in their fundi and were therefore classified as cases of malignant hypertension in agreement with the WHO criteria (16).

These 69 patients (41 men, 28 women) have been followed up until the end of 1977. Their average age was 46 years (range 16-74). Most patients (49, 71%) had IV retinopathy, while 20 (29%) had degree III retinopathy. After detailed clinical investigation

Table I Secondary hypertension (n=39)

	No of pats
<b>Renovascular disease (n=18)</b>	
Unilateral renal artery stenosis	12
Bilateral renal artery stenosis	5
Congenital anomaly	1
<b>Renoparenchymal disease (n=17)</b>	
Chronic pyelonephritis	6
Chronic glomerulonephritis	6
SLE nephritis	1
Congenital anomaly	1
Unspecified	3
<b>Endocrine disorders (n=4)</b>	
Phaeochromocytoma	2
Cushing's syndrome	1
Oestrogen (BC pill)	1

full laboratory work up, urography and in most cases also renal arteriography. 26 patients (38%) were considered to have essential hypertension. 39 (56%) secondary forms of hypertension (Table I) and in 4 cases (6%) a clear classification could not be made.

These patients were followed up until the end of 1977, particularly as regards survival rate. Special interest was devoted to conceivable prognostic indicators, such as initial BP and initial renal function. The survival curves were calculated by life table analysis.

## RESULTS

In this series of 69 patients with malignant hypertension, 19 (28%) died during the observation time. The causes of death were uraemia in 10 pa-

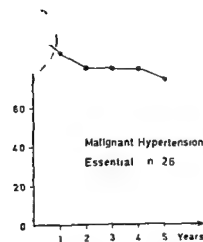


Fig 1 Survival rate in essential malignant hypertension

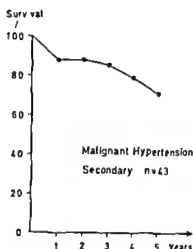


Fig 2 Survival rate in secondary (n=39) and unclassified (n=4) malignant hypertension

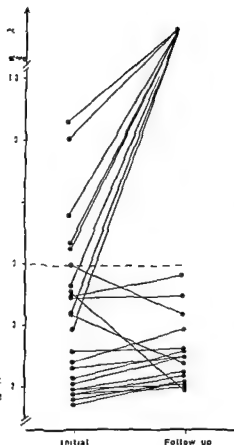
tients' sudden death/myocardial infarction in 4 miscellaneous in 5. No death was due to stroke.

The 5 year survival rate for the patients with malignant essential hypertension was 75% (Fig 1) and for those with secondary and unclassified malignant hypertension 72% (Fig 2).

Of the 26 patients with malignant essential hypertension, 20 had grade IV and 6 grade III retinopathy. None of the latter patients died during the observation period and none required therapy against uraemia. The 5 year survival for the patients with grade IV retinopathy was 60%. It should be noted that 4 of the latter patients underwent renal transplantation and one of them died during the surgical procedure. If renal transplantation had not been available, i.e. if the 5 surviving transplanted patients had died at the time of operation, the 5 year survival would have been 50%.

Table II Blood pressure (mmHg) at the time of diagnosis (mean  $\pm$  S.E.M.)

	Systolic BP	Diastolic BP
Essential hypertension (n=26)	252 $\pm$ 4	143 $\pm$ 3
Secondary hypertension (n=39)	232 $\pm$ 5	145 $\pm$ 3
Renovascular (n=18)	239 $\pm$ 8	148 $\pm$ 3
Renoparenchymal (n=17)	219 $\pm$ 5	138 $\pm$ 3
Endocrine (n=4)	248 $\pm$ 11	163 $\pm$ 11
Unclassified (n=4)	258 $\pm$ 16	150 $\pm$ 3



Change of serum creatinine in essential malignant hypertension ( $n=24$ ; data from 2 patients not available)

the patients with secondary malignant hypertension 6 with renoparenchymal disease received a transplant and 3 were treated with chronic dialysis. The patients with endocrine disorders (phaeochromocytoma and Cushing's syndrome) were treated surgically with good results. At the time of diagnosis all patients had markedly raised BPs (Table II). However, no correlation

Table III Symptoms at the time of diagnosis

	No. of pats
Hypertensive encephalopathy	4
Stroke	2
Focal neurological signs	6
Nausea/vomiting	12
Headaches	29
Blurred vision	25
Cardiac symptoms	17
Vertigo	4
Fatigue	9
Miscellaneous	3
No symptoms	4

could be found between the initial BP level and the prognosis *quo ad vitam*.

Among the patients with essential malignant hypertension renal function could be preserved or in some cases even improved in those who at the time of diagnosis had serum creatinine levels below  $100 \mu\text{mol/l}$ . Patients whose serum creatinine levels were above this arbitrary cut-off line all progressed towards uraemia in spite of antihypertensive therapy with three or more drugs (Fig. 3).

With only four exceptions all patients presented with one or more marked symptoms; in some cases severe neurological disorders; in the majority however complaints such as headaches, nausea and blurred vision (Table III). Another observation was the male preponderance, most clearly noted in the group with essential malignant hypertension. Thus 60% in the whole series were men against 69% in the group with essential malignant hypertension.

Finally a non-significant decrease ( $2 \times 8$  contingency table) in the annual incidence of malignant hypertension was seen during the observation period ( $p=0.15$ ) (Table IV). The entire decline came from essential malignant hypertension.

Table IV New cases of malignant hypertension

	1969	1970	1971	1972	1973	1974	1975	1976
Essential	5	4	5	2	3	2	3	2
	16				10			
Secondary	8	5	4	4	6	4	6	6
	21				22			

including 4 unclassified cases



T  
st  
sk  
m  
M  
m  
f  
E  
d  
d  
p  
m  
m  
h  
m  
r  
m  
b  
m  
r

## Adipose Tissue Cellularity—Metabolic Aspects

*The Population Study of Women in Göteborg 1974-1975*

Henry Noppa, Calle Bengtsson, Björn Isaksson and Ulf Smith

*From the Departments of Medicine II and Clinical Nutrition  
Sahlgrenska sjukhuset, University of Göteborg, Göteborg, Sweden*

**OBJECT** A representative population sample of middle aged women was studied in 1974-75. In a subsample body composition and adipose tissue cellularity variables were determined and individuals with a particular clinical disorder were compared with the total subsample. Women with diabetes mellitus had more body fat and higher fat cell weights and higher fat cell numbers, whereas these variables did not differ in women with IHD or hypertension. In the total subsample, total body fat correlated with arterial BPs, fasting blood glucose, serum lipids and serum uric acid. The correlations were stronger than those reported previously by us. In univariate analyses, fat cell weight correlated with systolic and diastolic BP, fasting blood glucose and serum uric acid, and fat cell number with diastolic BP. In multivariate analyses, when allowance was made for total body fat, the correlations between these variables and fat cell weight or number did not reach statistical significance.

**KEY WORDS:** adipose tissue, body fat, ischaemic heart disease, population, risk factors, women.

Med Scand 206: 501, 1979.

Obesity is defined as an excess amount of body fat. Enlargement of the adipose tissue mass is due to increased fat cell weight and/or number (8). Previous studies have suggested that changes in fat cell size rather than in fat cell number may be associated with aberrations in carbohydrate and lipid metabolism (10-13). Recently an association between fat cell weight and arterial blood pressure has also been suggested (9). Diabetes mellitus is associated with an increased incidence of ischaemic heart disease (IHD) (4, 30-34). Hence an association between fat cell weight and the incidence of IHD may also be expected.

A comprehensive study of the health status of middle aged women has been carried out in 1968-69 (5) and in 1974-75 (6). The study includes determination of a number of physiological and biochemical variables. In a subsample data were also obtained on body composition and adipose tissue cellularity.

The purpose of the present investigation was to study the relationships between total body fat, fat cell weight, fat cell number and various risk factors for IHD. For those who had IHD, diabetes mellitus or hypertension and who participated in the studies of body composition and adipose tissue cellularity, these data are also compared with the subsample representative of the general population.

## STUDY POPULATION

A population study of women was carried out in Göteborg, Sweden, in 1968-69 (5) and the participants were re-studied in 1974-75 (6). Altogether 1402 women (89.1% of those studied in 1968-69 or 80.3% of the initial sample) participated in the second study. Owing to the method of sampling, the high participation rate and the small differences between participants and non-participants, the women who participated on both occasions are regarded as representative of the women in the general population in the age strata studied (5, 6).

Body composition and adipose tissue cellularity studies in 1974-75 were carried out in a systematically selected subsample of 227 women, representative of the women in the general population in the age strata studied (44, 52, 56, 60 and 66 years of age). Of these women, 199 (87.7%) attended the primary examination comprising physical, anthropometric and laboratory investigations. 153 (67.4%) took part in the body composition study and 187 (82.4%) in the adipose tissue cellularity study. In the subsample, fat cell weight or fat cell number did not differ with age (4, 8), while body fat did, being higher in higher

Abbreviations: IHD=ischaemic heart disease, BP=blood pressure, BF=body fat, BW=body weight.

Table 1 Anthropometric data blood pressure and biochemical variables in the subsample and the total population sample of women

	Subsample			Total sample		
	n	Mean	S D	n	Mean	S D
BW (kg)	187	66.4	12.7	1301	65.8	11.4
Body height (cm)	187	163.0	5.7	1300	163.5	5.9
Triceps skinfold (mm)	187	21.5	7.0	1298	21.1	6.7
Subscapular skinfold (mm)	187	20.9	9.9	1298	20.5	10.0
Arm circumference (cm)	187	28.7	3.3	1296	28.4	3.0
Waist circumference (cm)	187	78.4	10.9	1297	77.7	10.1
Buttock circumference (cm)	187	99.1	8.9	1295	98.7	8.0
Systolic BP (mmHg)	187	140.0	22.2	1302	134.9	21.3
Diastolic BP (mmHg)	187	88.5	9.7	1302	87.3	9.8
Serum cholesterol (mmol/l)	185	7.1	1.3	1288	7.0	1.3
Serum triglycerides (mmol/l)	185	1.42	0.63	1288	1.30	0.88
Fasting blood glucose (mmol/l)	187	5.4	0.9	1298	5.3	0.9
Serum uric acid ( $\mu$ mol/l)	181	216	70	1292	204	66

age strata (26). The anthropometric data for the subsample did not differ from the total population sample (Table 1). Nor were there any differences in diastolic BP, serum cholesterol or fasting blood glucose, while systolic BP, serum triglyceride and serum uric acid levels were somewhat higher in the subsample than in the total sample (Table 1).

The correlation analyses between body composition, adipose tissue cellularity and the biochemical variables and BPs were confined to the 127 women for whom all data were available. Women with diabetes mellitus were excluded from the blood glucose analyses.

## METHODS

The women were asked to attend the primary examination after an overnight fast but were allowed to drink a moderate amount of water in the morning. The research staff was the same throughout the examination period in order to avoid interobserver variations in measurements.

Weight (BW) was measured to the nearest 0.1 kg. We wore only briefs when weighed. Body height was measured to the nearest 0.5 cm (27).

BP was measured with a mercury manometer as previously described (4). Serum cholesterol and triglycerides were determined according to a modification of the method of Franey and Amador (18) and Carlsson (14) respectively, and serum uric acid was determined according to the method of Gochman and Schmitz (19). Fasting blood glucose was determined as proposed by Hartman (20).

BF was derived from data for BW, total body potassium and total body water as described by Berg and Lissner (7). The methods are described elsewhere and are mentioned on together with the body composition data.

Adipose tissue samples were obtained by needle biopsy according to the method of Hirsch and Goldrick (2). The hypogastric region (one third of the distance from the right superior iliac spine to the umbilicus) and the femoral region (on the anterior side of the thigh, one third of the distance from the patella to the superior iliac spine) were selected. The adipose tissue samples were placed in physiological saline and frozen at  $-20^{\circ}\text{C}$  until fat cell weight determination. Mean fat cell weight in each region was determined according to the method of Sjostrom et al. (31). Total fat cell number was calculated by dividing total BF by the mean of the fat cell weights of the two regions.

## II Body composition and adipose tissue cellularity in women with different clinical disorders

	Total subsample			Myocardial infarction			Angina pectoris		
	n	Mean	S D	n	Mean	S D	n	Mean	S D
BW (kg)	187	66.4	12.7	4	64.4 NS	19.0	12	65.9 NS	15
BF mass (kg)	141	20.8	7.5	4	20.9 NS	9.9	10	22.1 NS	9
Mean fat cell weight ( $\mu$ g)	170	0.42	0.08	4	0.43 NS	0.11	10	0.45 NS	0
Total fat cell number ( $\times 10^7$ )	141	4.9	1.6	4	4.9 NS	2.4	8	4.4 NS	1

NS=no statistical significance \* $p<0.05$  \*\* $p<0.01$  \*\*\* $p<0.001$

II Correlations between body composition, adipose tissue cellularity and blood pressure and other variables in the women in whom both body composition and adipose tissue cellularity data were available ( $n=127$ )

	Fasting blood glucose	Serum cholesterol	Serum triglycerides	Systolic BP	Diastolic BP	Serum uric acid
Weight	0.28**	0.09 NS	0.16(*)	0.15(*)	0.26**	0.35***
Stature	0.26**	0.20*	0.22*	0.22*	0.30***	0.35*
Body fat	0.16(*)	0.14 NS	0.21	0.17(*)	0.14 NS	0.30**
Cell number	0.03 NS	0.14 NS	0.02 NS	0.20*	0.14 NS	0.15( )
	0.12 NS	0.16(*)	0.14 NS	0.21	0.16(*)	0.27**
	0.21**	0.16( )	0.17( )	0.12 NS	0.24*	0.22*

Note: Correlation coefficients. NS=no statistical significance. (\*) $p<0.10$ , \* $p<0.05$ , \*\* $p<0.01$ , \*\*\* $p<0.001$ .

of angina pectoris was recorded according to a score proposed by Rose (29). Myocardial infarction was recorded as described by Elmfeldt et al. (16). If arterial hypertension was obtained by interdiastolic hypertension was considered to be present if the patient was receiving antihypertensive treatment or if diastolic BP  $\geq 160$  mmHg and a diastolic BP  $\geq 95$  mmHg. Diabetes mellitus was considered to be present if the patient was receiving treatment for diabetes (diet or antidiabetic drug) or had laboratory signs of diabetes (fasting blood glucose concentration exceeding 11 mmol/L).

#### Methods

Standard statistical methods were used for calculation of means, standard deviations (SD), correlation coefficients and regression coefficients and significances of regression coefficients. The confounding effects of age and weight in the analyses of correlations between fat cell number and BP and biochemical variables were controlled by multiple regression analysis. Significant differences between mean values were tested with the *t*-test (two-tailed). When testing mean values with a particular clinical characteristic were compared with the total subsample. The differences and regression coefficients were considered statistically significant if  $p<0.05$ .

Illness	Arterial hypertension		
	SD	n	Mean
15.9	39	68.3	NS
9.7	30	22.6	NS
0.04	38	0.43	NS
1.6	29	5.0	NS

## RESULTS

### Body fat mass and adipose tissue cellularity in relation to IHD

Four of the women who participated in the adipose tissue cellularity study had suffered a myocardial infarction and 12 reported symptoms of angina pectoris. There were no significant differences in body composition or adipose tissue cellularity between these women and the total subsample (Table II).

### Body fat mass and adipose tissue cellularity in relation to risk factors for IHD

**Diabetes mellitus** Eight of the women who participated in the adipose tissue cellularity survey had diabetes mellitus. These women had higher mean values of BW ( $p<0.001$ ), BF ( $p<0.01$ ), mean fat cell weight ( $p<0.05$ ) and total fat cell number ( $p<0.05$ ) than the women in the total subsample (Table II).

**Hyperglycaemia** Fasting blood glucose correlated significantly with BW ( $p<0.01$ ), BF ( $p<0.01$ ) and total fat cell number ( $p<0.01$ ) (Table III). These correlations remained significant when allowance was made for the effect of age. When allowance was also made for BF in a multiple regression analysis the correlation between fat cell number and fasting blood glucose was not significant.

**Hyperlipidaemia** Serum cholesterol correlated significantly with BF ( $p<0.05$ ) but not with fat cell weight or total fat cell number (Table III). When allowance was made for the effect of age the correlation between serum cholesterol and BF was not significant.

Serum triglycerides correlated significantly

BF ( $p < 0.05$ ) and fat cell weight in the hypogastric region ( $p < 0.05$ ) but not with total fat cell number (Table III). The correlations remained significant when allowance was made for the effect of age. When allowance was also made for BF, the correlation between serum triglycerides and fat cell weight in the hypogastric region was not significant.

**Arterial hypertension** In the adipose tissue cellularity survey, 39 women had hypertension. There were no significant differences in body composition or adipose tissue cellularity between these women and the total subsample (Table II).

**Arterial blood pressure** Systolic BP correlated significantly with BF ( $p < 0.05$ ), fat cell weight in the femoral region ( $p < 0.05$ ) and mean fat cell weight ( $p < 0.05$ ) but not with total fat cell number (Table III). When allowance was made for the effect of age, these correlations were not significant. Diastolic BP correlated significantly with BF ( $p < 0.001$ ) and total fat cell number ( $p < 0.01$ ) but not with fat cell weight (Table III). These correlations remained significant when allowance was made for the effect of age. When allowance was also made for BF, the correlation between diastolic BP and fat cell number was not significant.

**Hyperuricaemia** None of the women in the adipose tissue cellularity survey had a history of gout. Serum uric acid correlated with BW ( $p < 0.001$ ), BF ( $p < 0.001$ ), fat cell weight in the hypogastric region ( $p < 0.001$ ), mean fat cell weight ( $p < 0.01$ ) and total fat cell number ( $p < 0.05$ ). These correlations remained significant when allowance was made for the effect of age. When allowance was also made for BF, the correlations between serum uric acid and the adipose tissue cellularity variables were not significant.

## DISCUSSION

### fat, IHD and risk factors for IHD

Earlier reports have suggested no or only a weak association between various estimates of obesity and IHD (22, 23, 30, 34). Similar results have been reported recently concerning the relationship between BF and IHD (35). The present data agree with these reports but the number of subjects with IHD is too low to allow conclusions. Multivariate analysis of data from prospective studies has shown that the effect of obesity on development of IHD is to a large extent mediated through coexisting atherogenic traits (22, 23). Increased BF mass was

also associated in the present study with raised serum lipids, fasting blood glucose as well as raised BP levels. The importance of an increased BF mass in diabetes, hyperlipidaemia and arterial hypertension is also suggested by the fact that weight reduction is accompanied by an improved glucose tolerance and reduced serum lipid and BP levels (3).

### Adipose tissue cellularity, IHD and risk factors for IHD

In this study an attempt was made to elucidate the relative contributions of fat cell weight and fat cell number to the associations discussed above.

A recent report has suggested an association between arterial hypertension and increased fat cell weight (9). We were not able to confirm this finding. As has also been reported in men (25), a correlation was found between fat cell weight and systolic BP but in the present study of women this correlation was not significant when allowance was made for the effect of age, which explained almost the entire variance of systolic BP. A recent study on obese women (2) revealed a correlation between fat cell number and diastolic BP. This finding was confirmed in the present study of randomly selected women. The correlations were significant in both studies when allowance was made for the effect of age.

Several haemodynamic changes have been reported in obesity, including increased cardiac output and increased peripheral arterial resistance. Furthermore, a correlation has been demonstrated between adipose tissue blood flow and fat cell number (15). Since fat cell number correlated with the diastolic BP, this factor may contribute to total peripheral resistance. However, in the present study none of the correlations remained statistically significant when BF was kept constant. In the previous study (2) allowance was not made for BF.

A previous report suggested that increased fat cell weight was associated with adult diabetes mellitus (12). The findings in the present study agree with this conclusion. However, fat cell weight has been shown to correlate weakly but significantly with plasma insulin levels in randomly selected middle-aged men (10) and in obese men and women (13). No such correlation was found initially in randomly selected women (10) but was demonstrated later for fat cell weight in the abdominal region but not for other regions (24). The data thus suggest that an increased fat cell weight is associated with

resistance. However, a recent study of men aged 40-59 years found no correlation between fat cell weight and fasting blood glucose or plasma insulin levels. The effect of BF was considered.

Cell weight has been found to be increased in hyperlipidaemic men and women (11). In these men a significant correlation has been demonstrated between serum triglycerides and fat cell weight (33). The present study of randomly selected middle-aged women showed a similar correlation for fat cell weight in the hypogastric but not in the femoral region. The observation that there are discrepancies in the relationships between the chemical variables measured and fat cell number in different regions may reflect regional variations, as has also been reported recently (12).

Overall, the present study shows stronger correlations between BF mass and arterial BP, serum fasting blood glucose and serum uric acid than were reported between weight index and these variables (27). The study also indicates that fat cell number is correlated to systolic BP and serum triglycerides, while fat cell number seems to correlate to diastolic BP and fasting blood glucose. The results clearly show that total BF is a stronger determinant of these variables than either fat cell weight or fat cell number alone. In epidemiological studies of large population samples it thus seems sufficient to study total BF rather than adipose tissue cellularity to evaluate the impact of obesity on

## ACKNOWLEDGEMENT

The study was supported by grants from the Swedish Research Council 27X-4578, 19X-570 and 03X-570.

## REFERENCES

- Anderson J K. Obesity and the circulation. *Mod Concepts Cardiovasc Dis* 32: 799, 1963.
- Jani F, Rossi F A, Ostuzzi R, Crivellini G, Nello O. Studies of blood pressure in obese subjects. Abstract. International Symposium on Medical Complications of Obesity, p. 49, June 15-16, 1978, Rome, Italy.
- Wahlberg H W Jr & Kannel W B. Relation of weight to changes in atherogenic traits. The Framingham study. *J Chronic Dis* 27: 103, 1974.
- Jonsson C. Ischaemic heart disease in women. A study based on a randomized population sample of 40- and 50-year-old women with myocardial infarction in Sweden. *Acta Med Scand (Suppl)* 549.
- Bengtsson C, Blohmé G, Hallberg L, Hallström T, Isaksson B, Korsan Bengtson K, Rybo G, Tibblin E, Tibblin G & Westerberg H. The study of women in Gothenburg 1968-1969—a population study. General design, purpose and sampling results. *Acta Med Scand* 193: 311, 1973.
- Bengtsson C, Hallberg L, Hallström T, Hultborn A, Isaksson B, Lennartsson J, Lindquist O, Lindstedt S, Noppa H, Redvall L & Samuelsson S. The population study of women in Göteborg 1974-1975—the second phase of a longitudinal study. General design, purpose and sampling results. *Scand J Soc Med* 6: 49, 1978.
- Berg K & Isaksson B. Body composition and nutrition of school children with cerebral palsy. *Acta Paediatr Scand (Suppl)* 204: 41, 1970.
- Björntorp P. Disturbances in the regulation of food intake. Obesity: anatomic and physiologic-biochemical observations. *Adv Psychosom Med* 7: 116, 1972.
- The fat cell. A clinical view. Second International Congress on Obesity, October 23-26, 1977, Washington, USA.
- Björntorp P, Bengtsson C, Blohmé G, Jonsson A, Sjöström L, Tibblin E, Tibblin G & Wilhelmsson L. Adipose tissue fat cell size and number in relation to metabolism in randomly selected middle-aged men and women. *Metabolism* 20: 927, 1971.
- Björntorp P, Gustavsson A & Persson B. Adipose tissue fat cell size and number in relation to metabolism in endogenous hypertriglyceridemia. *Acta Med Scand* 190: 363, 1971.
- Björntorp P, Jonsson A & Berchtold P. Adipose tissue cellularity in maturity onset diabetes mellitus. *Acta Med Scand* 191: 129, 1972.
- Björntorp P & Sjöström L. Number and size of adipose tissue fat cells in relation to metabolism in human obesity. *Metabolism* 20: 703, 1971.
- Carlson L A & Wadström L B. Determination of glycerides in blood serum. *Clin Chim Acta* 4: 197, 1959.
- DiGirolamo M & Esposito J. Adipose tissue blood flow and cellularity in the growing rabbit. *Am J Physiol* 229: 107, 1975.
- Elmfeldt D, Wilhelmsson L, Tibblin G, Vedin J A, Wilhelmsson C E & Bengtsson C. Registration of myocardial infarction in the city of Göteborg, Sweden. A community study. *J Chronic Dis* 28: 173, 1975.
- Epstein F H & Ostrander L D. Detection of individual susceptibility towards coronary disease. *Prog Cardiovasc Dis* 13: 324, 1971.
- Franey R J & Amador E. Serum cholesterol measurement based on ethanol extraction and ferric-chloride-sulphuric acid. *Clin Chim Acta* 21: 255, 1968.
- Gochman N & Schmitz J M. Automated determination of uric acid with use of a uricase peroxidase system. *Clin Chem* 17: 1154, 1971.
- Hartel A, Helger R & Lang H. Die Blutzuckerbestimmung mit der o-Toluidin-Methode ohne Eis. *Z. Klin Chem* 7: 14, 1969.
- Hirsch J & Goldnick R B. Serial st

- metabolism of human adipose tissue. I. Lipogenesis and free fatty acid uptake and release in small aspirated samples of subcutaneous fat. *J Clin Invest* 43: 1776-1964.
- 22 Kannel W B & Gordon T. Obesity and cardiovascular disease. The Framingham study. In: *Obesity* (ed W L Burland, P D Sammel & J Yudkin) pp 24-51. Churchill Livingstone, London, 1974.
  - 23 Keys A, Aravanis C, Blackburn H, van Buchem F S P, Buzina R, Djordjevic B S, Fidanza F, Karvonen M J, Menotti A, Puddu V & Taylor H L. Coronary heart disease. Overweight and obesity as risk factors. *Ann Intern Med* 77: 15, 1972.
  - 24 Krotkiewski M, Sjöström L, Björntorp P & Smith U. Regional adipose tissue cellularity in relation to metabolism in young and middle aged women. *Metabolism* 24: 703, 1975.
  - 25 Larsson B. Obesity. A population study of men with special reference to development and consequences for the health. Thesis. University of Göteborg. Gotab Kungälv, 1978.
  - 26 Noppa H, Andersson M, Bengtsson C, Bruce A & Isaksson B. Body composition in middle aged women with special reference to the correlation between body fat mass and anthropometric data. *Am J Clin Nutr* 32: 1388, 1979.
  - 27 Noppa H, Bengtsson C, Björntorp P, Smith U & Tibblin E. Overweight in women—metabolic aspects. The population study of women in Göteborg, 1968-1969. *Acta Med Scand* 203: 135, 1978.
  - 28 Noppa H, Bengtsson C, Isaksson B & Smith U. Adipose tissue cellularity in adulthood and its relation to childhood obesity. The population study of women in Göteborg, 1974-1975. *Int J Obesity* (submitted for publication, 1979).
  - 29 Rose G A. The diagnosis of ischaemic heart and intermittent claudication in field survey. *WHO* 27: 645, 1962.
  - 30 Rosenman R H, Brand R J, Sholtz R, Friedman M. Multivariate prediction of coronary heart disease during 8.5 year follow up in the Coronary Collaborative Group study. *Am J Cardiol* 1976.
  - 31 Sjöström L, Björntorp P & Vrána J. Microfat cell size measurements on frozen-cut adipose tissue in comparison with automatic determination of osmium fixed fat cells. *J Lipid Res* 12: 571, 1971.
  - 32 Smith U, Björntorp P, Hammarsten J & G. Regional differences and effect of diet on human fat cell metabolism. *Eur J Clin Invest* (in press, 1979).
  - 33 Stern M P, Olefsky J, Farquhar J W & Liss G M. Relationship between fasting plasma glucose levels and adipose tissue morphology. *Metabolism* 22: 1311, 1973.
  - 34 Tibblin G, Wilhelmsen L & Werkö L. Risk factors for myocardial infarction and death due to ischaemic heart disease and other causes. *Arch Intern Med* 135: 514, 1975.
  - 35 Weinsier R L, Fuchs R J, Kay T D, Tser J H & Lancaster M C. Body fatness, relationship to coronary heart disease, blood pressure and other risk factors measured in a large population. *Am J Med* 61: 815, 1976.

# Hyperparathyroidism Associated with Distal Tubular Dysfunction with Intact Reabsorption of Protein in the Proximal Tubules

Lars Wibell Per Anders Dahlberg and Anders Karlsson

*From the Department of Internal Medicine University Hospital Uppsala Sweden*

**T**he urinary output of  $\beta_2$ -microglobulin was measured in ten hypercalcemic patients undergoing surgery because of hyperparathyroidism. In five subjects the  $\beta_2$ -microglobulin excretion was increased and in seven patients it was normal. Before surgery three of these seven patients displayed markedly impaired distal tubular function with a reduced urinary concentration capacity. After surgery all patients became normocalcemic. Urinary concentrating capacities improved and  $\beta_2$ -microglobulin excretion on the other hand remained unchanged. Thus, hypercalcemia per se does not readily affect the proximal tubular function. Impaired low molecular weight proteins "Tubular proteinuria", if found in patients with hyperparathyroidism, should be suspected to reflect damage to the tubules by additional mechanisms.

**Key words:** hyperparathyroidism, hypercalcemia,  $\beta_2$ -microglobulin, kidney function.

Acta Med Scand 206 507 1979

Hyperparathyroidism (HPT) is sometimes associated with kidney dysfunction in general attributed to diffuse calcium nephropathy (8). When glomerular filtration rate is impaired (14, 18) it improves after parathyroidectomy. In contrast to the common impairment of the renal concentrating ability is often reversed after correction of hypercalcemia (7, 11).

It has been claimed (6) that a selective urinary excretion of low molecular weight (LMW) proteins, termed proteinuria, can be present in patients with HPT—and be reversible during the months after parathyroidectomy. Hayslett et al (13) described three hyperparathyroid subjects with normal serum creatinine values and increased excretion of lysozyme (mol wt 14000). Revillard

et al (20) have found mixed proteinuric patterns by electrophoresis of urinary protein in five patients with parathyroid adenomas.

We have investigated the influence of hypercalcemia on the proximal renal tubules by following the urinary output of  $\beta_2$ -microglobulin in patients undergoing surgery because of HPT.  $\beta_2$ -microglobulin (mol wt 11800) first isolated from the urine of patients with renal tubular disorders (4) is one of the major LMW proteins of tubular proteinuria and as such a sensitive marker of protein reabsorption in the proximal renal tubules (19, 23).

## PATIENTS

Ten patients with hypercalcemia and probable HPT were selected for the study. Patients with a history of recurrent kidney stones or infections in the urinary pathways were excluded since obstruction and infection, particularly if connected with hypercalcemia or renal tubular acidosis, may be associated with an abnormal excretion of LMW proteins (5, 12, 13, 15). In seven of the patients a diagnosis of HPT was not suspected until a routine serum calcium determination was performed and disclosed a high value. Patients 3 and 8 had suffered single episodes of renal colic. These patients and patient 9 had minimal kidney calcifications at urography. Patient 5 had a non-functioning left kidney after a complicated nephrolithotomy 15 years ago. In all other patients X-ray investigations of the kidneys were normal.

Laboratory findings are presented in Table 1. Pronounced hypercalcemia was present in patients 1-3 and moderate hypercalcemia in two of the other seven subjects. Most patients had an increased phosphate excretion and when tested in patients 5-10 pathological urine phosphate responses to calcium infusion as in HPT (22) were found in five cases. The ability to produce concentrated urine was subnormal in all subjects and markedly low urinary osmolalities were noted after pitressin tannate administration in patients 1-3. Serum alkaline phosphatase

**Abbreviations:** HPT = hyperparathyroidism, LMW = low molecular weight.



Table 1 Laboratory findings

With the exception of tubular reabsorption of phosphate (TRP) and maximal osmolality the laboratory data represent mean of 2-5 determinations

Pat no	Sex	Age (y)	S-Ca (mmol/l)		U Ca (mmol/24 h)	Max osmol <sup>a</sup> (mOsm/kg)	S-creat (μmol/l)	C <sub>creat</sub> (ml/min/1.73 m <sup>2</sup> )	S-P (mg/l)
			Preop	Postop <sup>*</sup>					
1	♀	53	3.4	2.3	15	375	82	80	0.6
2	♀	51	3.3	2.4	17	530	70	120	0.6
3	♀	52	3.1	2.3	15	465	72	140	0.7
4	♀	73	3.0	3.5	5	670	110	70	0.8
5 <sup>a</sup>	♂	66	3.0	2.5	2	630	187	45	0.8
6	♀	72	2.9	2.5	4	690	83	60	0.8
7	♀	68	2.9	2.3	10	600	75	70	0.8
8	♀	26	2.9	2.4	8	780	75	115	0.8
9	♂	64	2.9	2.3	6	680	76	95	0.8
10	♀	69	2.8	2.4	3	710	106	55	0.5
Reference values			2.2-2.6		0.6-5.0	>750	64-106	75-140	0

<sup>a</sup> Determined 5 months after surgery

<sup>b</sup> Determined with a Knauer Osmometer. Urine collected after water restriction and injection of pitressin tannate

<sup>c</sup> Determined after infusion of calcium (22). N = normal, P = pathological

<sup>d</sup> This patient, who had only one functioning kidney, displayed moderate proteinuria (0.5 g albumin/24 h) and a glomerular filtration rate

was slightly elevated in two patients. X-ray investigations of the skeleton revealed an unequivocal bone disease in patient 10 with osteopenia and subperiosteal erosions. Vascular calcifications of the Moenchberg type (21) were apparent in patient 3.

The diagnosis of HPT was corroborated in all patients by thorough examination of removed parathyroid tissues. Expert evaluation of parathyroid glands was performed by L. Grimelius. Single adenomas were found in 9 patients, one of whom also had two hyperplastic glands; one patient had two hyperplastic and two normal glands. Postoperatively, the levels of serum and urinary calcium were normalized in all patients. When investigated five months postoperatively, the urinary concentration ability after pitressin tannate administration was improved in all ten patients, although in six patients the values of urinary osmolality were still subnormal, in the range of 650-750 mOsm/kg.

## METHODS

$\beta_2$ -Microglobulin was determined with a radioimmunoassay kit (9) (Phadebas Pharmacia, Uppsala). All other analyses were carried out with the routine procedures in use at the Laboratory of Clinical Chemistry, University Hospital, Uppsala. Only single urine specimens with a pH above 5.8 were accepted for study, since at low pH degradation of  $\beta_2$ -microglobulin frequently occurs (10). Urines were stored at -20°C until analysis. The urinary excretion of  $\beta_2$ -microglobulin was expressed as a ratio of  $\beta_2$ -microglobulin to creatinine in order to minimize the variation among samples caused by differences in diuresis (23).

## RESULTS AND DISCUSSION

The urinary  $\beta_2$ -microglobulin/creatinine ratio before parathyroidectomy during the postoperative 1 day and at the follow-up five months postoperatively are shown in Fig. 1. Before surgery, the excretion of  $\beta_2$ -microglobulin was of normal magnitude in seven patients. Three of these patients (nos. 1-3) had the most pronounced hypercalcaemia and hypercalciuria, and the lowest maximal tubular osmolality after pitressin tannate administration. At the follow-up, these seven patients had a microglobulin excretion similar to that found before the operation. Thus, patients with HPT may have hypercalcaemia, hypercalciuria, and a reduced concentrating capacity but still retain a normal capacity for reabsorption of LMW proteins in the proximal renal tubules.

Three of the investigated patients (cases 5, 6, and 10) had an abnormal excretion of  $\beta_2$ -microglobulin. It is clear that the amount of  $\beta_2$ -microglobulin in urine of these cases did not correlate to the serum calcium level or to the maximal urinary osmolality. This supports the concept that an impaired concentrating capacity is secondary to hypercalcaemia and in part due to functional changes rather than to structural alterations and microscopic calcinosis in the kidney (3, 8, 11).

After Ca <sup>++</sup>	S alk phosph ( $\mu$ kat/l)
-	4.5
-	4.5
-	4.3
-	2.6
73 N	2.2
87 P	6.4
77 P	3.4
83 P	2.1
86 P	8.6
77 P	5.5

0.8-4.8

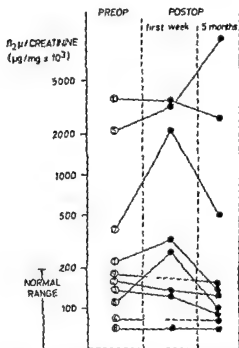


Fig 1 Urinary excretion of  $\beta_2$  microglobulin before and after parathyroidectomy in ten patients with primary HPT. The data are presented as the ratio of  $\beta_2$ -microglobulin/creatinine.

temporary postoperative increase in the  $\beta_2$  globulin excretion was observed in three patients (6 and 7). This finding may be analogous to the high excretion of LMW proteins observed in patients after major surgical intervention and in patients with large burns (1). The mechanism of such proteinuria is not known. Possible postoperative catabolic phase induces a release of the kidney of LMW substances. Such release could interfere with proximal tubular reabsorption in much the same way as an infusion of amino acids causes tubular proteinuria (17). Previous reports (6, 13, 20) on LMW proteinuria in patients with HPT: no details were given concerning renal stones or associated kidney disease in patients with kidney stones but without proteinuria. Surprisingly high incidence—up to 80%—of proteinuria has been reported as lysozymuria, hyperinsulinuria (5). In the latter of these reports all patients had spinal cord injuries. Thus, pyelonephritis is likely to have been a confounding factor. In a recent study of consecutive patients with recurrent stone disease seen in our patient clinic (2) less than 10% of the patients displayed an elevated excretion of  $\beta_2$ -microglobulin. These results suggest that hypercalcemia per se

does not interfere with the protein reabsorbing capacity of the kidney tubules. As reabsorption of filtered proteins mainly occurs in the proximal tubules (16) our findings are consistent with the observations that pathological calcifications in hypercalcemia first occur in the distal part of the nephron, such as the collecting ducts and the ascending limb of Henle's loop (8). Clearly tubular proteinuria is not an early or obligatory finding in patients with HPT. When LMW proteinuria is found a complicating kidney disorder should be looked for.

#### ACKNOWLEDGEMENT

This study was supported by a grant from Tore Nilsson Foundation.

#### REFERENCES

1. Arturson G, Evrin P E & Wibell L. Renal function studies in patients with extensive burn. *Medicinsk Riksstämman* 1973; Svenska Läkaresällskapet Stockholm Abstract K140:196, 1973.

- 2 Backman U, Danielsson B G & Sothell M Urinary excretion of  $\beta_2$ -microglobulin in renal stone patients under normal conditions and during acidosis and alkalosis. *Scand J Urol Nephrol (Suppl)* 35: 79, 1976
- 3 Bech N, Singh H, Reed S W, Mordangh H V & Davis B B Pathogenic role of cyclic AMP in the impairment of urinary concentrating ability in acute hypercalcemia. *J Clin Invest* 54: 1049, 1974
- 4 Berggård I & Bearn A G Isolation and properties of a low molecular weight  $\beta_2$ -globulin occurring in human biological fluids. *J Biol Chem* 243: 4095, 1968
- 5 Chung K N, Karam J H, Choy F B, Kolb F O, Grodsky G M & Forsham P H Hypernephroma in patients with renal calculi. *Clin Chim Acta* 52: 383, 1972
- 6 Dent C E The Balkan nephropathy (ed G E Wolstenholme and J Knight) p 108. Ciba Foundation, Boston, 1967
- 7 Edvall C A Renal function in hyperparathyroidism. *Acta Chir Scand (Suppl)* 229, 1958
- 8 Epstein F H Calcium and the kidney. *Am J Med* 45: 700, 1968
- 9 Evrin P E, Peterson P A, Wide L & Berggård I Radioimmunoassay of  $\beta_2$ -microglobulin in human biological fluids. *Scand J Clin Lab Invest* 28: 439, 1971
- 10 Evrin P E & Wibell L The serum level of  $\beta_2$ -microglobulin in apparently healthy subjects. *Scand J Clin Lab Invest* 29: 69, 1972
- 11 Gill J R & Bartter F C On the impairment of renal concentration ability in prolonged hypercalcemia and hypercalciuria in man. *J Clin Invest* 40: 716, 1961
- 12 Hall P W & Vasiljevic M  $\beta_2$ -microglobulin excretion as an index of renal tubular disorders with special reference to endemic Balkan nephropathy. *J Lab Clin Med* 81: 897, 1973
- 13 Hayslett J P, Penlie P E & Finch S C Urinary muramidase and renal disease. *N Engl J Med* 279: 506, 1968
- 14 Hellström J, Birke G & Edvall C A Hypertension in hyperparathyroidism. *Br J Urol* 30: 13, 1958
- 15 Kregzde J, Lamberg L L & Davidson Lysozymuria in renal calculus following surgical injury. *Urol Int* 24: 310, 1969
- 16 Maunsbach A B Ultrastructure and digestivity of lysosomes from proximal tubular cells. *Proc 4th Int Congr Nephrol*, vol 1, pp 11. Karger, Basel, 1969
- 17 Mogensen C E, Solling K & Vittinghus Increased urinary excretion of albumin light chain  $\beta_2$ -microglobulin after intravenous arginine administration in normal man. *Lancet* 2: 581, 1975
- 18 Olsson L Primary hyperparathyroidism in 160 patients. University of Gothenburg, Gothenburg, 1975
- 19 Peterson P A, Evrin P E & Berggård I Differentiation of glomerular tubular and normal renal determinations of urinary excretion of  $\beta_2$ -microglobulin, albumin and total protein. *J Clin Invest* 48: 1189, 1969
- 20 Revillard J P, Manuel Y, Francois R & Tardieu J Renal diseases associated with tubular proteinuria. In: *Proteins in normal and pathological urine* (ed J P Manuel, J P Revillard and H Betuel), pp 207-217. Karger, Basel, 1970
- 21 Taiter G L V, Baillod R A, Varghese Z, W B Farrow S, Wills M R & Moorhead Evolution of bone disease over 10 years in 100 patients with terminal renal failure. *Br Med J* 1: 1173, 1973
- 22 Wibell L, Johansson H & Werner I The calcium infusion test in the diagnosis of hyperparathyroidism. *Scand J Clin Lab Invest* 30: 183, 1972
- 23 Wibell L & Karlsson F A The urinary excretion of  $\beta_2$ -microglobulin after the induction of a diuresis: a study in healthy subjects. *Nephron* 17: 343, 1976
- 24 Wide L & Thoren L Increased urinary excretion of albumin,  $\beta_2$ -microglobulin, insulin and luteal hormone following surgical or accidental hyperparathyroidism. *Scand J Clin Lab Invest* 30: 275, 1972

# Labetalol-Induced Peyronie's Disease?

## A Case Report

Bent Østergaard Kristensen

From Medical Department P Randers City Hospital  
University Hospital of Aarhus Randers Denmark

The Peyronie's disease (induratio penis) has been observed in a 58-year old man after initiation of treatment with the new  $\alpha$  and  $\beta$  blocking agent, labetalol. During months before onset of symptoms he had 200 mg labetalol daily. He showed no other normal fibrous tissue production and the as negative. Cessation of the drug revealed the Peyronie's disease. This disease has also been in relation to treatment with propranolol and metoprolol and might be due to an imbalance between  $\alpha$  and  $\beta$  receptors in the penis, but there may also be an immunological basis for the fibrosis. A possible coincidence as the ages of the reported cases are within the range where this disease most often develops.

Peyronie's disease  $\beta$  blockers labetalol  
and 206 511 1979

The disease or induratio penis plastica is a local fibrous tissue production on the shaft of the penis. Although several suggestions have been made its aetiology is unknown (2, 11). The syndrome was in some cases associated with normal fibrous tissue production in the penile cavity (3, 6) and recently Peyronie's disease has been observed in relation to treatment with propranolol (7, 12) and metoprolol (14).

Caution should always be paid to new drugs to avoid undesired reactions. For instance, in relation to the practolol syndrome. As we have observed the development of Peyronie's disease in connection with the combined  $\alpha$  and  $\beta$  blocking agent labetalol we would like to report this

case of a patient with severe and resistant hypertension. He had been treated for several years with methyldopa and diuretics. Treatment with labetalol was initiated with 100 mg t.i.d. and the dose was titrated against BP response and side-effects. His symptoms began 8 months after his entry to the study. At that time he had been treated with labetalol 2400 mg/day for 2 months. The disease made him unable to perform sexual intercourse while it did not interfere with micturition. The plaque measured 1x3 cm and was located on the left dorsolateral side of the shaft, easily palpable.

Cessation of the drug did not result in any improvement. Further clinical and laboratory investigations showed no signs of abnormal fibrous tissue production elsewhere in the body, especially he had no oculomucocutaneous eruptions or Dupuytren's contracture and the ANF test was negative.

## DISCUSSION

The age of our patient and of those cited above (7, 8, 12) is within the range when Peyronie's disease most often develops. The observation of this disease in relation to treatment with  $\beta$  blocking agents may therefore be a coincidental finding without any association to the drugs employed. Moreover, atherosclerosis has been suggested to be an aetiological factor in Peyronie's disease (11) and as hypertension is one of the main risk factors for atherosclerotic disorders, this disease might have contributed to the development of Peyronie's disease.

On the other hand Pryor and Khan (8) very lately reported their results from a review of 146 patients with Peyronie's disease. Of these patients 19 (13.1%) had been treated with a  $\beta$  blocking agent against none of the age matched controls without this disease. Of the 19 patients 7 had been receiving practolol and 13 propranolol, including one patient on both drugs for at least six months before the onset of penile discomfort. The mean age of the patients was 55 years (range 25-72), but naturally no information is given either

## CASE HISTORY

A 58-year-old man was admitted to a long-term treatment on the efficacy of labetalol in the manage-

the patients on  $\beta$  blocking agents or whether they had concomitant atherosclerotic diseases or hypertension. However, the findings in this large series seem to suggest a relationship between therapy with  $\beta$  blocking agents and onset of Peyronie's disease in some patients.

Although the practolol syndrome is well established including the sclerosing conditions, it is still unknown whether the abnormal fibrous tissue production is due to an impaired balance between  $\alpha$  and  $\beta$  receptors in connective tissue or there may be an immunological basis for the fibrosis. Amos et al. (1) observed that practolol metabolites provoked antibody production, and a positive ANF test was associated with this syndrome (4, 10). A positive ANF test has also been encountered during treatment with labetalol (9). The ANF test was negative in our patient, and in this context it must be stressed that a positive ANF test does not necessarily imply drug induction. Positive ANF tests have been found as often in untreated as in treated hypertensive patients (5) and significantly more often in untreated hypertensive patients than in normotensive controls (5, 13).

The observation of Peyronie's disease in connection with treatment with non-selective (propranolol (7, 8, 12)), cardioselective (metoprolol (14)) and practolol (8)) and combined  $\alpha$  and  $\beta$  blocking agents (labetalol) thus might suggest that an altered balance between  $\alpha$  and  $\beta$  receptors contributes to an abnormal fibrous tissue production. However, a provocation of antibody formation induced by molecular structural similarities between these drugs or their metabolites cannot be ruled out.

As labetalol is about to be introduced to Scandinavian antihypertensive drug markets, clinicians are asked to pay attention to this problem.

# ADDENDUM

Eight months after cessation of Labetalol treatment, the fibrous plaque had diminished markedly and the patient was again able to perform sexual intercourse.

# REFERENCES

- 1 Amos H E, Lake B G & Aris J. *Br Med J* 402 1978
- 2 Bilig R, Baker R, Immergut M & Maive. *Urology* 6 409 1975
- 3 Eltingham W K. *Lancet* i 843 1977
- 4 Felix R H, Ivy F A & Dah M C G. *Br Med J* 321 1974
- 5 Kristensen B Ø & Andersen P L. *Acta Scand* 203 55 1978
- 6 Marshall A J, Baddely H, Barrett D W, Lee R E, J Low Beer T G & Read Q J. *Med* 146 181 1977
- 7 Osborne D R. *Lancet* i 1111 1977
- 8 Pryor J P & Khan O. *Lancet* i 331 1979
- 9 Pugsley D J, Armstrong B K, Nassim M, Beilin L J. *Br J Clin Pharmacol (Suppl)* 3 777
- 10 Raftery E B & Denmann A M. *Br Med J* 1973
- 11 Smith G H. *Am J Clin Pathol* 45 670 1965
- 12 Wallis A A, Bell R & Sutherland P W. *Br Med J* 2 980 1977
- 13 Wilson J D, Bullock J Y & Booth R J. *Br Med J* 2 996 1978
- 14 Yudkin J S. *Lancet* ii 1355 1977

## SUPPLEMENTS TO VOLUME 206

- 630 Application and evaluation of automated arrhythmia monitoring in the coronary care unit  
By J. Hulting
- 631 Essential fatty acids in chronic alcoholism. By C. Alling, G. Aspenstrom, S. J. Dencker and  
L. Svennerholm
- 632 Renal function in hypercalcemia. A clinical and experimental study. By L. E. Lins
- 633 Myocardial enzyme release in coronary bypass and valve replacement surgery. Clinical studies  
with special reference to the serum activity of creatine kinase MB isoenzyme. By S. Strom
- 634 The cardiovascular disease study in Norwegian counties. Background and organization. By  
A. Bjartveit, O. P. Foss, T. Gjervig and P. G. Lund-Larsen
- 635 Metabolism of plasma and biliary lipids in hyperlipoproteinaemia. By B. Leijed

# SUBJECT INDEX

(Supplements see p v)

## Adipose tissue

- Adipose tissue cellularity—Metabolic aspects (Noppa Bengtsson Isaksson & Smith) 501

## Adrenals

- Effects on muscle electrolytes of potassium and magnesium infusions spironolactone medication and operation in a case of primary aldosteronism (Dyckner & Wester) 137  
The role of endogenous cortisol in patients with non thyroidal illness and decreased  $T_3$  levels (Kallner & Ljunggren) 459

## Alcohol

- Metabolic effects of glucocorticoid and ethanol administration in phenformin and metformin treated obese diabetics (Schaffalitzky de Muckadell Mortensen & Lyngsoe) 269  
Clinical significance of abnormal heterogeneity of transferrin in relation to alcohol consumption (Stubler Borg & Allgulander) 275

## Amino acids

- Amino acid metabolism in patients with a hereditary myopathy and paroxysmal myoglobinuria (Wahren Linderholm & Felig) 309

## Amyloidosis

- Free light chains of immunoglobulins in amyloidosis (Sølling & Sølling) 283

## Anaemia

- Pernicious anaemia as a risk factor in gastric cancer (Elsborg & Mosbech) 315

## Anticoagulants

- Comparison of streptokinase with heparin Late results in the treatment of deep venous thrombosis (Johansson Nylander Hedner & Nilsson) 93

## Arrhythmia

- Mortality arrhythmias and pump failure in acute myocardial infarction in relation to estimated infarct size (Nordlander & Nyquist) 65  
Diastolic wave initiating ventricular tachyarrhythmias and suppressible by lignocaine and isoprenaline (Orninus) 127  
Sick sinus syndrome treated with permanent pacemaker in 109 patients (Brevik Ohm & Segadal) 153  
Arrhythmias in the coronary care unit recognized with the aid of automated ECG monitoring (Hulting) 177  
Myocardial infarction complicated by heart block—Treatment and long term prognosis (Forsberg & Juul Møller) 483

## Arteries

- Work status after coronary bypass surgery (Frick Hargola & Valle) 61  
Q waves and coronary artery disease (Fischer Hansen & Pedersen Bjergaard) 193

Familial occurrence of intracranial aneurysms (Stavenow)	197
Temporal arteritis and gangrene of the tongue (Amung & Lind Nielsen)	239
Effect of physical training on different categories of patients with intermittent claudication (Jonason Jonzon Ringqvist & Öman Rydberg)	253
Late sudden death after surgical correction of coarctation of the aorta (Forfang Rostad Sorland & Levorstad)	375
Non invasive methods in the evaluation of obliterative disease of the subclavian or innominate artery (Ekstrom Eklund Liljeqvist & Nordhus)	467
<b>Arteriography</b>	
Coronary arteriography in 486 patients—Arteriographic pathology and prognosis (Ljungberg Forsberg Paulin & Werko)	145
<b>Biopsy</b>	
Bone biopsy in women with spinal osteoporosis (Hulth Nilsson Westlin & Wiklund)	205
<b>Blood</b>	
Changes in serum triglyceride and cholesterol levels during long term phenytoin treatment for epilepsy (Luoma Reunanen & Sotaniemi)	229
Isochromosome 17 in a patient with a myeloproliferative disorder terminating in eosinophilic leukemia (Lönngqvist Gahrton Eriksson Enberg & Zech)	321
Isovolemic hemodilution in erythrocytosis secondary to chronic obstructive lung disease (Danielson & Nordenstrom)	327
Serum ferritin during inflammation A study on myocardial infarction (Birgegård Hallgren Venge & Wide)	361
Diagnostic sign of hyperglycemia. Persistent movement of neutrophil granules (Juhlin & Shelley)	447
<b>Blood pressure</b>	
Blood pressure in 60-year-old men (Waern & Åberg)	99
Influence of a myocardial infarction on blood pressure and serum cholesterol (McCall Elmfeldt Vedin Wilhelmsson Wedel & Wilhelmsen)	477
<b>Bone</b>	
Small cell carcinoma of the lung Relation of calcitonin to bone marrow metastases parathormone and gastrin (Hansen Rehfeld & Stadil)	215
<b>Brain</b>	
Familial occurrence of intracranial aneurysms (Stavenow)	197
<b>Cancer</b>	
Pernicious anaemia as a risk factor in gastric cancer (Elsborg & Mosbech)	315
<b>Cancer of the lung</b>	
Small cell carcinoma of the lung Relation of calcitonin to bone marrow metastases parathormone and gastrin (Hansen Rehfeld & Stadil)	215
<b>Catecholamines</b>	
Non selective and selective $\beta$ 1 adrenoceptor blocking agents in the treatment of hyperthyroidism (Nüsön Karlberg Kågedal Tegler & Almqvist)	



## VIII *Subject index*

### Chromosomes

- Inactivation of one of the X chromosomes in females is a biological phenomenon of clinical importance (Editorial) 1  
 Isochromosome 17 in patient with a myeloproliferative disorder terminating in eosinophilic leukemia (Lonnqvist Gahrton Eriksson Friberg & Zech) 371

### Circulation

- Central and renal circulation renin and aldosterone in plasma during prazosin treatment in essential hypertension (Falch Quist Paulsen Ødegaard & Norman) 489

### Complement

- Systemic capillary leak syndrome with monoclonal IgG and complement alterations (Lofdahl Solvell Laurell & Johansson) 405

### Diabetes mellitus

- Glibenclamide and glipizide maturity onset diabetes (Blohmé & Waldenström) 263  
 Metabolic effects of glucocorticoid and ethanol administration in phenformin and metformin treated obese diabetics (Schaffalitzky de Muckadell Mortensen & Lyngsøe) 269

### Diagnosis

- The diagnostic challenge of left atrial myxoma (Berning Egeblad Lauridsen & Wennevold) 115  
 Massive embolization of cardiac myxoma (Tornvall & Olin) 123  
 Arrhythmias in the coronary care unit recognized with the aid of automated ECG monitoring (Hulting) 177  
 Q waves and coronary artery disease (Fischer Hansen & Pedersen Bjergaard) 193  
 Erythrocyte sedimentation rate in a population sample of women with special reference to its clinical and prognostic significance (Rafnsson Bengtsson Lennartsson Lindquist Noppa & Tibblin) 207  
 Miliary tuberculosis (Stenius Aarnala & Tukiainen) 417  
 An atypical manifestation of multiple myeloma in a 24-year-old male (Wille Wetteland Förre Hovig & Winnem) 423  
 Noninvasive diagnosis of acute deep vein thrombosis (Watz Ek & Bygdeman) 463  
 Non invasive methods in the evaluation of obliterative disease of the subclavian or innominate artery (Ekstrom Eklund Liljeqvist & Nordhus) 467

### ECG

- The Q-T syndrome—A family description (Andersson & Lundkvist) 73  
 Arrhythmias in the coronary care unit recognized with the aid of automated ECG monitoring (Hulting) 177  
 Q waves and coronary artery disease (Fischer Hansen & Pedersen Bjergaard) 193  
 Effect of plasma free fatty acid lowering on exercise tolerance and ST segment depression in patients with angina pectoris (Loogna Kaijser & Carlsson) 371

### Electrolytes

- Electrolytes and whole body potassium in acute leukemia (Lantz Carlmark & Feizenstem) 45  
 Effects on muscle electrolytes of potassium and magnesium infusions spironolactone medication and operation in a case of primary aldosteronism (Dyckner & Wester) 137

**Enzymes**

- Angiotensin-converting enzyme in sarcoidosis (Rømer) 27
- The effects of a beta<sub>1</sub> blocking agent atenolol on blood pressure plasma renin activity and prostaglandin F<sub>2a</sub> excretion in patients with essential hypertension (Pitkajarvi Ylitalo Metsa Ketela & Vapaatalo) 107
- Alkaline phosphatase in women with osteoporosis (Hulth Nilsson Westlin & Wiklund) 201
- Procainamide induced lupus erythematosus like syndrome in relation to acetylator phenotype and plasma levels of procainamide (Sonnag Karlsson & Hed) 245

**Epilepsy**

- Changes in serum triglyceride and cholesterol levels during long term phenytoin treatment for epilepsy (Luoma Reunanen & Sotaniemi) 229

**Erythrocytes**

- Isovolemic hemodilution in erythrocytosis secondary to chronic obstructive lung disease (Danielson & Nordenstrom) 327

**Fatty acids**

- Effect of plasma free fatty acid lowering on exercise tolerance and ST segment depression in patients with angina pectoris (Loogna Kajser & Carlson) 371

**Gastrointestinal tract**

- Pernicious anaemia as a risk factor in gastric cancer (Elsborg & Mosbech) 315
- Reduced vibratory perception and corneal sensitivity and metabolic disturbances following intestinal bypass surgery (Hey Vesti Nielsen Lund Lund & Sørensen) 391

**Glucose**

- Effect of 24-hour somatostatin infusion on glucose homeostasis and on the levels of somatomedin A and pancreatic and thyroid hormones in man (Lins Efendic & Hall) 441
- Diagnostic sign of hyperglycemia Persistent movement of neutrophil granules (Juhlin & Shelley) 447

**Goitre**

- Function of pituitary thyroid axis after surgical treatment of non toxic nodular goitre (Blichert Toft Egedorf Christiansen & Axelsson) 15

**Heart**

- Emergency room resuscitation of patients with cardiac arrest outside hospital (Erhardt Sederholm & Gertz) 55
- Work status after coronary bypass surgery (Frick Harjola & Valle) 61
- Mortality arrhythmias and pump failure in acute myocardial infarction in relation to estimated infarct size (Nordlander & Nyquist) 65
- Carditis associated with mycoplasma pneumoniae infection (Ponka) 77
- The diagnostic challenge of left atrial myxoma (Berning Egeblad Lauridsen & Wennevold) 115
- Massive embolization of cardiac myxoma (Tornvall & Ohlén) 123
- Diastolic wave initiating ventricular tachyarrhythmias and suppressible by lignocaine and isoprenaline (Orninus)
- Coronary arteriography in 486 patients—Arteriographic pathology and prognosis (Ljunger Forsberg Paulm & Werkö)
- Aortic valve replacement in elderly patients (Storstein & Efskind)

Prognosis in hypertrophic obstructive cardiomyopathy (Orninus)	289
Late sudden death after surgical correction of coarctation of the aorta (Forfang Rostad Sörlund & Levorstad)	375
Oesophageal symptoms and manometry in valvular heart disease (Tibbling & Wranne)	381
Disopyramide plasma levels in cardiac patients on maintenance therapy (Landmark Störsten & Larsen)	385
Diet lipids and heart attacks (Werko)	435
Incidence and significance of heartmuscle antibodies in patients with acute myocardial infarction and unstable angina (Liem ten Veen Lie Felkamp & Durrer)	473
<b>Heredity</b>	
Inactivation of one of the X chromosomes in females is a biological phenomenon of clinical importance (Editorial)	1
Relationship between biochemical and clinical features in an English Anderson Fabry family (Hamers Wise Eijofor Strijland Robinson & Tager)	5
The Q-T syndrome—A family description (Andersson & Lundkvist)	73
Familial occurrence of intracranial aneurysms (Stavenow)	197
Procainamide induced lupus erythematosus like syndrome in relation to acetylator phenotype and plasma levels of procainamide (Sonnag Karlsson & Hed)	245
Amino acid metabolism in patients with a hereditary myopathy and paroxysmal myoglobinuria (Wahren Linderholm & Felig)	309
<b>Hormones</b>	
T <sub>4</sub> , T <sub>3</sub> and reverse T <sub>3</sub> determinations in connection with the TRH test in the evaluation of possible hyperthyroidism (Kallner & Ljunggren)	11
Function of pituitary thyroid axis after surgical treatment of non toxic nodular goitre (Blichert Toft Egedorf Christiansen & Axelsson)	15
Effects on muscle electrolytes of potassium and magnesium infusions spironolactone medication and operation in a case of primary aldosteronism (Dyckner & Wester)	137
The syndrome of inappropriate secretion of antidiuretic hormone (Hagg Lithner Lundqvist & Fjhrquist)	141
Small cell carcinoma of the lung Relation of calcitonin to bone marrow metastases parathyroid hormone and gastrin (Hansen Rehfeld & Stadil)	215
Streptozotocin treatment of a pancreatic tumour producing VIP and gastrin associated with Verner Morrison syndrome (Öberg Bostrom Fahrenkrug Dyming Schaffhitzky de Muckadell & Lundqvist)	223
Effect of 24-hour somatostatin infusion on glucose homeostasis and on the levels of somatomedin A and pancreatic and thyroid hormones in man (Lins Efendić & Hall)	441
The role of endogenous cortisol in patients with non thyroidal illness and decreased T <sub>3</sub> levels (Kallner & Ljunggren)	459
and renal circulation renin and aldosterone in plasma during prazosin treatment in essential hypertension (Falch Quist Paulsen Ødegaard & Norman)	489
Hyperparathyroidism associated with distal tubular dysfunction but intact reabsorption of protein in the proximal tubules (Wibell Dahlberg & Karlsson)	507
<b>Hypertension</b>	
Angiotensin-converting enzyme in sarcoidosis (Rømer)	27
The effects of a beta <sub>1</sub> blocking agent atenolol on blood pressure plasma renin activity and prostaglandin F <sub>2α</sub> excretion in patients with essential hypertension (Pitkärä Ylitalo Metsä Ketela & Vapaatalo)	107
Atenolol administered once daily in primary hypertension (Nilsson Karlberg Ohlsson Thulin & Tolagen)	303
Central and renal circulation renin and aldosterone in plasma during prazosin treatment in essential hypertension (Falch Quist Paulsen Ødegaard & Norman)	489
Malignant hypertension—Improving prognosis in a rare disease (Gudbrandsson Hansson Herlitz & Andrén)	495

**Immunity**

- Immune complex glomerulonephritis in chronic granulomatous disease (van Rhenen Koolen Feltkamp-Vroom & Weening) 233

**Immunoglobulins**

- Systemic capillary leak syndrome with monoclonal IgG and complement alterations (Löfdahl Solvell Laurell & Johansson) 405
- Rheumatoid arthritis immune complex disease and hypereosinophilic syndrome (Hillerdal Marjanovic & Åberg) 429

**Infection**

- Carditis associated with mycoplasma pneumoniae infection (Ponkä) 77

**Intoxication**

- Multiple attacks of jaundice associated with repeated sulfonamide treatment (Iwarson & Lundin) 219
- Changes in serum triglyceride and cholesterol levels during long term phenytoin treatment for epilepsy (Luoma Reunanen & Sotaniemi) 221
- Procainamide induced lupus erythematosus like syndrome in relation to acetylator phenotype and plasma levels of procainamide (Sonnag Karlsson & Hed) 245

**Iron metabolism**

- Clinical significance of abnormal heterogeneity of transferrin in relation to alcohol consumption (Stibler Borg & Allgulander) 275

**Kidney**

- Relationship between biochemical and clinical features in an English Anderson Fabry family (Hamers Wise Eijfor Strjland Robinson & Tager) 5
- Angiotensin-converting enzyme in sarcoidosis (Rømer) 27
- The effects of a beta<sub>1</sub> blocking agent atenolol on blood pressure plasma renin activity and prostaglandin F<sub>2a</sub> excretion in patients with essential hypertension (Pitkärjä Ylitalo Metsä Ketelä & Vapaatalo) 107
- Immune complex glomerulonephritis in chronic granulomatous disease (van Rhenen Koolen Feltkamp-Vroom & Weening) 233
- Central and renal circulation renin and aldosterone in plasma during prazosin treatment in essential hypertension (Falch Quist Paulsen Ødegård & Norman) 489
- Hyperparathyroidism associated with distal tubular dysfunction but intact reabsorption of protein in the proximal tubules (Wibell Dahlberg & Karlsson) 507

**Leukaemia**

- The expression of a human B lymphocyte antigen on cells in different types of leukaemia (Tureson Berntorp & Zettervall) 31
- The expression of a human B lymphocyte antigen and surface membrane immunoglobulin by lymphoid cells from patients with lymphocytic lymphoma multiple myeloma and benign monoclonal gammopathy (Tureson Berntorp & Zettervall) 17
- Electrolytes and whole body potassium in acute leukemia (Lantz Carlmark & Reizenste
- Isochromosome 17 in a patient with a myeloproliferative disorder terminating in co leukemia (Lönngqvist Gahrton Eriksson Finberg & Zech)

Prognosis in hypertrophic obstructive cardiomyopathy (Orninus)	289
Late sudden death after surgical correction of coarctation of the aorta (Forfang Rostad Sörland & Levorstad)	375
Oesophageal symptoms and manometry in valvular heart disease (Tibbling & Wranne)	381
Disopyramide plasma levels in cardiac patients on maintenance therapy (Landmark Storstein & Larsen)	385
Diet lipids and heart attacks (Werkö)	435
Incidence and significance of heartmuscle antibodies in patients with acute myocardial infarction and unstable angina (Laem ten Veen Lie Feltkamp & Durrer)	473

## Heredity

Inactivation of one of the X chromosomes in females is a biological phenomenon of clinical importance (Editorial)	1
Relationship between biochemical and clinical features in an English Anderson Fabry family (Hamers Wise Ejsiofor Stryland Robinson & Tager)	5
The Q-T syndrome—A family description (Andersson & Lundkvist)	73
Familial occurrence of intracranial aneurysms (Stavenow)	197
Procainamide induced lupus erythematosus like syndrome in relation to acetylator phenotype and plasma levels of procainamide (Sonnhaag Karlsson & Hed)	245
Amino acid metabolism in patients with a hereditary myopathy and paroxysmal myoglobinuria (Wahren Landerholm & Felig)	309

## Hormones

T <sub>4</sub> T <sub>3</sub> and reverse T <sub>3</sub> determinations in connection with the TRH test in the evaluation of possible hyperthyroidism (Kallner & Ljunggren)	11
Function of pituitary thyroid axis after surgical treatment of non toxic nodular goitre (Blichert Toft Egedorf Christiansen & Axelsson)	15
Effects on muscle electrolytes of potassium and magnesium infusions spironolactone medication and operation in a case of primary aldosteronism (Dyckner & Wester)	137
The syndrome of inappropriate secretion of antidiuretic hormone (Hagg Lithner Lindqvist & Fyhrquist)	141
Small cell carcinoma of the lung Relation of calcitonin to bone marrow metastases parathyroid hormone and gastrin (Hansen Rehfeld & Stadil)	215
Streptozotocin treatment of a pancreatic tumour producing VIP and gastrin associated with Verner Morrison syndrome (Öberg Bostrom Fahrenkrug Dymling Schaffalitzky de Muckadell & Lundqvist)	223
Effect of 24-hour somatostatin infusion on glucose homeostasis and on the levels of somatomedin A and pancreatic and thyroid hormones in man (Lins Efendić & Hall)	441
The role of endogenous cortisol in patients with non thyroidal illness and decreased T <sub>4</sub> levels (Kallner & Ljunggren)	459
Central and renal circulation renin and aldosterone in plasma during prazosin treatment in essential hypertension (Falch Quist Paulsen Ødegaard & Norman)	489
Hyperparathyroidism associated with distal tubular dysfunction but intact reabsorption of protein in the proximal tubules (Wibell Dahlberg & Karlsson)	507

## Hypertension

Angiotensin-converting enzyme in sarcoidosis (Rømer)	27
The effects of a beta <sub>1</sub> blocking agent atenolol on blood pressure plasma renin activity and prostaglandin F <sub>2α</sub> excretion in patients with essential hypertension (Pitkajarvi Ylitalo Metsä Keitela & Vapaatalo)	107
Atenolol administered once daily in primary hypertension (Nilsson Karlberg Ohlsson Thulin & Tolagen)	203
Central and renal circulation renin and aldosterone in plasma during prazosin treatment in essential hypertension (Falch Quist Paulsen Ødegaard & Norman)	489
Malignant hypertension—Improving prognosis in a rare disease (Gudbrandsson Hansson Herlitz & Andrén)	495

**Immunity**

- Immune complex glomerulonephritis in chronic granulomatous disease (van Rhenen Koolen Feltkamp-Vroom & Weening) 233

**Immunoglobulins**

- Systemic capillary leak syndrome with monoclonal IgG and complement alterations (Löfdahl Solvell Laurell & Johansson) 405
- Rheumatoid arthritis immune complex disease and hypereosinophilic syndrome (Hillerdal Marjanovic & Åberg) 429

**Infection**

- Carditis associated with mycoplasma pneumoniae infection (Ponkä) 77

**Intoxication**

- Multiple attacks of jaundice associated with repeated sulfonamide treatment (Iwarson & Lundin) 219
- Changes in serum triglyceride and cholesterol levels during long term phenytoin treatment for epilepsy (Luoma Reunanen & Sotaniemi) 229
- Procainamide induced lupus erythematosus like syndrome in relation to acetylator phenotype and plasma levels of procainamide (Sonnag Karlsson & Hed) 245

**Iron metabolism**

- Clinical significance of abnormal heterogeneity of transferrin in relation to alcohol consumption (Stibler Borg & Allgulander) 275

**Kidney**

- Relationship between biochemical and clinical features in an English Anderson Fabry family (Hamers Wise Eijofor Stryland Robinson & Tager) 5
- Angiotensin-converting enzyme in sarcoidosis (Rømer) 27
- The effects of a beta<sub>1</sub> blocking agent atenolol on blood pressure plasma renin activity and prostaglandin F<sub>2a</sub> excretion in patients with essential hypertension (Pitkälä Järvi Ylitalo Metsä Ketela & Vapaatalo) 107
- Immune complex glomerulonephritis in chronic granulomatous disease (van Rhenen Koolen Feltkamp-Vroom & Weening) 233
- Central and renal circulation renin and aldosterone in plasma during prazosin treatment in essential hypertension (Falch Quist Paulsen Ødegaard & Norman) 489
- Hyperparathyroidism associated with distal tubular dysfunction but intact reabsorption of protein in the proximal tubules (Wibell Dahlberg & Karlsson) 507

**Leukaemia**

- The expression of a human B lymphocyte antigen on cells in different types of leukaemia (Turesson Bernthorp & Zettervall) 31
- The expression of a human B lymphocyte antigen and surface membrane immunoglobulin on lymphoid cells from patients with lymphocytic lymphoma multiple myeloma and benign monoclonal gammopathy (Turesson Bernthorp & Zettervall) 31
- Electrolytes and whole body potassium in acute leukemia (Lantz Carlmark & Reizenstein) 31
- Isochromeosome 17 in a patient with a myeloproliferative disorder terminating in leukemia (Lonnqvist Gahrton Enksson Friberg & Zech) 31

## Subject index

### Leucocytes

- Induced neutropenias in the Stockholm region 1976-1977 (Arneborn & Palmblad) 241
- Effect of prolonged *in vivo* administration of leukocyte interferon on the mitogen responsiveness of human lymphocytes (Einhorn, Blomgren, Cantell & Strander) 345
- Rheumatoid arthritis, immune complex disease and hypereosinophilic syndrome (Hillerdal, Marjanovic & Åberg) 429
- Diagnostic sign of hyperglycemia: Persistent movement of neutrophil granules (Juhlin & Shelley) 447
- Effect of sulfasalazine and its active components on human polymorphonuclear leukocyte function in relation to ulcerative colitis (Molin & Stendahl) 451

### Lipids

- Changes in serum triglyceride and cholesterol levels during long term phenytoin treatment for epilepsy (Liloma, Reunanen & Sotaniemi) 229
- Diet, lipids and heart attacks (Werko) 435
- Influence of myocardial infarction on blood pressure and serum cholesterol (McCall, Elmfeldt, Edin, Wilhelmsson, Wedel & Wilhelmsen) 477

### Liver

- Multiple jaundice: Jaundice associated with repeated sulfonamide treatment (Iwarson & Lundin) 219

### Lung

- Isovolemic hemodilution in erythrocytosis secondary to chronic obstructive lung disease (Danielson & Nordenstrom) 327

### Lymphocytes

- The expression of a human B lymphocyte antigen on cells in different types of leukaemia (Turesson, Berntorp & Zettervall) 31
- The expression of a human B lymphocyte antigen and surface membrane immunoglobulin by lymphoid cells from patients with lymphocytic lymphoma, multiple myeloma and benign monoclonal gammopathy (Turesson, Berntorp & Zettervall) 37
- Prognostic significance of lymphopenia in sarcoidosis (Selroos & Koivunen) 259
- Effect of prolonged *in vivo* administration of leukocyte interferon on the mitogen responsiveness of human lymphocytes (Einhorn, Blomgren, Cantell & Strander) 345

- Relief of pruritus as an early sign of spinal cord compression in Hodgkin's disease (Olsson & Brandt) 319

### Metabolism

- Relationship between biochemical and clinical features in an English Anderson-Fabry family (Harners, Wise, Eijofor, Stryland, Robinson & Tager) 5
- Electrolytes and whole body potassium in acute leukemia (Lantz, Carlmark & Reizenstem) 45
- The effects of a beta blocking agent, atenolol, on blood pressure, plasma renin activity and prostaglandin  $F_{2\alpha}$  excretion in patients with essential hypertension (Pitkäranta, Ylitalo, Meckel, Ketela & Vapaatalo) 107
- Alkaline phosphatase in women with osteoporosis (Hulth, Nilsson, Westlin & Wiklund) 201
- Bone biopsy in women with spinal osteoporosis (Hulth, Nilsson, Westlin & Wiklund) 205
- Amino acid metabolism in patients with a hereditary myopathy and paroxysmal myoglobinuria (Wahren, Linderholm & Felg) 229

Reduced vibratory perception and corneal sensitivity and metabolic disturbances following intestinal bypass surgery (Hey Vesti Nielsen Lund Lund & Sorensen)	391
Ultrastructure of the microvessels in skeletal muscle in a case of systemic capillary leak syndrome (Johansson & Lofdahl)	413
Adipose tissue cellularity—Metabolic aspects (Noppa Bengtsson Isaksson & Smith)	501

## Mortality

Mortality arrhythmias and pump failure in acute myocardial infarction in relation to estimated infarct size (Nordlander & Nyquist)	65
--	----

## Muscles

Myasthenia gravis and Werlhof's disease (Veenhoven Oosterhuis & van der Schans)	131
Prognosis in hypertrophic obstructive cardiomyopathy (Orninus)	289
Amino acid metabolism in patients with a hereditary myopathy and paroxysmal myoglobinuria (Wahren Linderholm & Felig)	309
Ultrastructure of the microvessels in skeletal muscle in a case of systemic capillary leak syndrome (Johansson & Lofdahl)	413

## Myeloma

The expression of a human B lymphocyte antigen and surface membrane immunoglobulin by lymphoid cells from patients with lymphocytic lymphoma multiple myeloma and benign monoclonal gammopathy (Turesson Berntorp & Zettervall)	37
An atypical manifestation of multiple myeloma in a 24-year-old male (Wille Wetteland Forre Hovig & Winnem)	423

## Myocardial infarction

Mortality arrhythmias and pump failure in acute myocardial infarction in relation to estimated infarct size (Nordlander & Nyquist)	65
A controlled study of early discharge after uncomplicated myocardial infarction (Ahlmärk Ahlberg Saetre Haglund & Korsgren)	87
Prediction of survival in patients with acute myocardial infarction (Björck Erhardt & Lindberg)	165
Early mobilization and discharge of patients with acute myocardial infarction (Lindvall Erhardt Lundman Rehnqvist & Sjogren)	169
Intraaortic balloon pumping in the treatment of cardiogenic shock complicating acute myocardial infarction (Forssell Nordlander Nyquist & Schenck-Gustavsson)	189
Myocardial infarction in Malmo during the 10-year period 1963–1972 (Isacsson & Johansson)	293
Dobutamine in left heart failure after acute myocardial infarction (Rehnqvist & Lundman)	299
Risk factors for myocardial infarction in the Stockholm prospective study (Carlson Bottiger & Ahfeldt)	351
Serum ferritin during inflammation A study on myocardial infarction (Burgegård Hallgren Venge & Wide)	361
Clinical features in patients with recurrent myocardial infarction (Lofmark)	367
Effect of plasma free fatty acid lowering on exercise tolerance and ST segment depression in patients with angina pectoris (Loogna Kayser & Carlsson)	371
Incidence and significance of heartmuscle antibodies in patients with acute myocardial infarction and unstable angina (Liem ten Veen Lie Felkamp & Durrer)	473
Influence of a myocardial infarction on blood pressure and serum cholesterol (McCall Elmteklit Vedin Wilhelmsson Wedel & Wilhelmssen)	477
Myocardial infarction complicated by heart block—Treatment and long term prognosis (Forberg & Juul Moller)	



# **Nervous system**

- Relief of pruritus as an early sign of spinal cord compression in Hodgkin's disease (Olsson & Brandt) 319
- Reduced vibratory perception and corneal sensitivity and metabolic disturbances following intestinal bypass surgery (Hey-Vest, Nielsen, Lund, Lund & Sørensen) 391

# **Obesity**

- Metabolic effects of glucocorticoid and ethanol administration in phenformin and metformin treated obese diabetics (Schaffalitzky de Muckadell, Mortensen & Lyngsøe) 269

# **Oesophagus**

- Oesophageal symptoms and manometry in valvular heart disease (Tibblin & Wranne) 381

# **Pacemaker**

- Sick sinus syndrome treated with permanent pacemaker in 109 patients (Breivik, Ohm & Segadal) 153

# **Pancreas**

- Streptozotocin treatment of a pancreatic tumour producing VIP and gastrin associated with Verner-Morrison syndrome (Öberg, Boström, Fahrenkrug, Dymling, Schaffalitzky de Muckadell & Lundqvist) 223
- Effect of 24-hour somatostatin infusion on glucose homeostasis and on the levels of somatomedin A and pancreatic and thyroid hormones in man (Lins, Elfendic & Hall) 441

# **Paraneoplasia**

- The syndrome of inappropriate secretion of antidiuretic hormone (Hagg, Lithner, Lundqvist & Fyhrquist) 141
- Small cell carcinoma of the lung. Relation of calcitonin to bone marrow metastases, parathormone and gastrin (Hansen, Rehfeld & Stadil) 215

# **Parathyroid**

- Hyperparathyroidism associated with distal tubular dysfunction but intact reabsorption of protein in the proximal tubules (Wibell, Dahlberg & Karlsson) 407

# **Poisoning**

- Self poisoning treated in the ICU (Heath & Selander) 51

# **Population studies**

- Blood pressure in 60-year-old men (Waern & Åberg) 99
- Erythrocyte sedimentation rate in a population sample of women with special reference to its clinical and prognostic significance (Rafnsson, Bengtsson, Lennartsson, Lindqvist, Norrby & Tibblin) 207
- Drug induced neutropenias in the Stockholm region 1976-1977 (Arneborn & Palmblad) 241
- Myocardial infarction in Malmö during the 10-year period 1963-1972 (Isacsson & Johansson) 293
- Stroke registration in Göteborg, Sweden 1970-75 (Harmsen, Berglund, Larsson, Tibblin & Wilhelmson) 337
- Risk factors for myocardial infarction in the Stockholm prospective study (Carlson, Borstger & Åhfeldt) 341
- Incidence of urolithiasis leading to hospitalization in Finland (Juuti & Hemonen) 397

## Prognosis

- Coronary arteriography in 486 patients—Arteriographic pathology and prognosis (Jöngholm Forsberg Paulin & Werkö)
- Prediction of survival in patients with acute myocardial infarction (Börckert, Trolldenier & Lindha)
- Erythrocyte sedimentation rate in a population sample of women with special reference to clinical and prognostic significance (Rafnsson, Bengtsson, Lennartsson, Lindqvist, Nilsson & Tibblin)
- Prognostic significance of lymphopenia in sarcoidosis (Selroos & Kuvshinov)
- Prognosis in hypertrophic obstructive cardiomyopathy (Onnäs)
- Risk factors for myocardial infarction in the Stockholm prospective study (Cahlin, Blomgren, Ahlfeldt)
- Late sudden death after surgical correction of coarctation of the aorta (Erfang, Kistner, Land & Levorstad)
- Deaths and heart attacks (Werkö)
- Myocardial infarction complicated by heart block—Treatment and long-term prognosis (Jönberg & Juul-Möller)
- Malignant hypertension—Improving prognosis in a rare disease (Gödtansson, Jönsson, Herlitz & Andren)

## Proteins

- The expression of a human B lymphocyte antigen and surface membrane in lymphoid cells from patients with lymphocytic lymphoma, multiple myeloma and clonal gammopathy (Turesson, Berntorp & Zettervall)
- Immune complex glomerulonephritis in chronic granulomatous disease (van Boven, Veltkamp-Vroom & Weening)
- Clinical significance of abnormal heterogeneity of transferrin in relation to disease (Ståhl, Borg & Allgulander)
- Free light chains of immunoglobulins in amyloidosis (Solling & Sævi)
- Serum ferritin during inflammation. A study on myocardial infarction (Venge & Wide)
- Rheumatoid arthritis, immune complex disease and hypertension (Marjanovic & Åberg)

## Pulse

- Diastolic wave in left ventricular tachyarrhythmias and isoprenaline (Onnäs)

## Renal stones

- Incidence of urolithiasis leading to hospitalization in Finland (Järvelin, Järvelin & Järvelin)

## Rheumatoid arthritis

- Rheumatoid arthritis, immune complex disease and hypertension (Marjanovic & Åberg)

## Sarcoidosis

- Angiotensin-converting enzyme in sarcoidosis (Rømer)
- Prognostic significance of lymphopenia in sarcoidosis (Selroos & Kuvshinov)

## Skeleton

- Alkaline phosphatase in women with osteoporosis (Huhtala)
- Bone biopsy in women with spinal osteoporosis (Huhtala)

# Nervous system

- Relief of pruritus as an early sign of spinal cord compression in Hodgkin's disease (Olsson & Brandt) 319
- Reduced vibratory perception and corneal sensitivity and metabolic disturbances following intestinal bypass surgery (Hey-Vest, Nielsen, Lund, Lund & Sørensen) 391

# Obesity

- Metabolic effects of glucocorticoid and ethanol administration in phenformin- and metformin-treated obese diabetics (Schaffalitzky de Muckadell, Mortensen & Lyngsøe) 269

# Oesophagus

- Oesophageal symptoms and manometry in valvular heart disease (Tibblin & Wranne) 381

# Pacemaker

- Sick sinus syndrome treated with permanent pacemaker in 109 patients (Breivik, Ohm & Segadal) 153

# Pancreas

- Streptozotocin treatment of a pancreatic tumour producing VIP and gastrin associated with Verner-Morrison syndrome (Öberg, Boström, Fahrenkrug, Dymling, Schaffalitzky de Muckadell & Lundqvist) 223
- Effect of 24-hour somatostatin infusion on glucose homeostasis and on the levels of somatomedin A and pancreatic and thyroid hormones in man (Lins, Efendić & Hall) 441

# Paraneoplasia

- The syndrome of inappropriate secretion of antidiuretic hormone (Hägg, Lithner, Lindqvist & Fyhrquist) 141
- Small cell carcinoma of the lung: Relation of calcitonin to bone marrow metastases, parathormone and gastrin (Hansen, Rehfeld & Stadil) 715

# Parathyroid

- Hyperparathyroidism associated with distal tubular dysfunction but intact reabsorption of protein in the proximal tubules (Wibell, Dahlberg & Karlsson) 407

in the ICU (Heath & Selander) 51

blood pressure in 60-year-old men (Waern & Åberg) 99

Erythrocyte sedimentation rate in a population sample of women with special reference to its clinical and prognostic significance (Rafnsson, Bengtsson, Lennartsson, Lindqvist, Noppa & Tibblin) 707

Drug-induced neutropenias in the Stockholm region 1976-1977 (Arneborn & Palmblad) 241

Myocardial infarction in Malmö during the 10-year period 1963-1972 (Isacsson & Johansson) 293

Stroke registration in Göteborg, Sweden, 1970-75 (Harmsen, Berglund, Larsson, Tibblin & Wilhelmssen) 337

Risk factors for myocardial infarction in the Stockholm prospective study (Carlson, Böttiger & Åhfeldt) 351

Incidence of urolithiasis leading to hospitalization in Finland (Juuti & Heinonen) 397

# OF AUTHORS

- 1.99 479  
 P E 351  
 G 87  
 LG 87  
 de C 275  
 Suppl 631  
 S 21  
 on P 73  
 L 495  
 P 241  
 K 239  
 om G Suppl 631  
 C K 15  
 on C 501  
 I  
 AG 337  
 J 115  
 E 31 37  
 G 165  
 d G 361  
 k Suppl 634  
 Toft M 15  
 G 63  
 n H 345  
 L E 1  
 S 775  
 m H 22  
 L 319  
 L K 153  
 an S 463  
 K 345  
 rk B 45  
 L A 351  
 anen C 15  
 P A 507  
 on M 37  
 er S J Suppl 6  
 D 473  
 er T 13  
 g J F 3  
 S 441  
 M L 161  
 d H 115  
 n S 345  
 A 5  
 463  
 om S 46  
 B 467  
 D 477
- Elsborg L 315  
 Erhardt L R 55 165 169  
 Eriksson P 371  
 Fahrenkrug J 223  
 Fal h D K 489  
 Felg P 309  
 Felkamp T E W 473  
 Feltkamp-Vroom T M 233  
 Fischer Hansen J 193  
 Forre O 43  
 Forfang K 375  
 Forsberg S Å 145 483  
 Forssell G 189  
 Foss O P Suppl 634  
 Friberg K 371  
 Frick M H 61  
 Fyhrquist F 141  
 Gahrton G 371  
 Gertz I 55  
 Gjervig T Suppl 634  
 Gudbrandsson T 495  
 Hagg E 141  
 Halgren R 361  
 Hagrd 1 87  
 H 41  
 Hatters M N 5  
 Hansen M 15  
 Hansson L 495  
 Harjola P T 61  
 Harmsen P 337  
 Heath A 51  
 Hed J 45  
 Hedner L 93  
 Heimonen O P 397  
 Hertiz H 495  
 Hey H 191  
 Hillerdal G 479  
 Hoig T 43  
 Huith A G 201 205  
 Hultung J 177 Suppl 630  
 Isacson S-O 793  
 Isaksson B 501  
 Iwarson S 19  
 Johansson B W 793  
 Johansson B R 405 413  
 Johansson L 93  
 Jonason T 53  
 Jonzon B 53  
 Juhan L 447
- Juul Moler S 483  
 Juuti M 397  
 Kagedal B 21  
 Kayser L 371  
 Kallner G 11 419  
 Karlberg B E 21 303  
 Karlson A 407  
 Karlsson E 45  
 Koivunen E 259  
 Koolen M I 233  
 Korsgren M 87  
 Landmark A 385  
 Lantz B 45  
 Larsen A 385  
 Larsson O 337  
 Laurell A-B 405  
 Laursen P 115  
 Leyd B Suppl 635  
 Levorstad K 375  
 Loe A I 473  
 Lom K L 473  
 Liljeqvist L 467  
 Lindberg G 165  
 Linderholm H 309  
 Lind Nielsen I 239  
 Lindqvist B 141  
 Lindvall K 169  
 Lins L E Suppl 632  
 Lins P E 441  
 Lithner F 141  
 Ljungberg S 145  
 Ljunggren J-G 11 459  
 Löfdahl C-G 405 413  
 Lofmark R 367  
 Lonnqvist B 31  
 Loogna E 371  
 Lund B 391  
 Lund Bj 391  
 Lund n P 719  
 Lundkvist L 73  
 Lund Larsen P G Suppl 634  
 Lundman T 169 799  
 Lundqvist G 23  
 Luoma P A 229  
 Lyngsøe J 469  
 Maganovic B 479  
 McCall M 477  
 Metsä-Ketela T 107  
 Molin L 451  
 Mortensen H 269  
 Mosbeck J 313

XX *List of authors*

- |                             |                            |                      |
|-----------------------------|----------------------------|----------------------|
| Nilsson B E 201 205         | Saetre H 87                | Valle M 61           |
| Nilsson I M 93              | Schaffalitzky de Muckadell | Vapaatalo H 107      |
| Nilsson O R 21 303          | O B 223 269                | Vedin A 477          |
| Noppa H 501                 | van der Schans G S 131     | ten Veen J H 473     |
| Nordenström J 327           | Schenck Gustavsson A 189   | Veenhoven W A 131    |
| Nordhus O 467               | Sederholm M 55             | Venge P 361          |
| Nordlander R 65 189         | Segadal L 153              | Vesti Nielsen N 391  |
| Norman N 489                | Selander, D 51             |                      |
| Nylander G 93               | Selroos O 259              |                      |
| Nyquist O 65 189            | Shelley W B 447            | Waern U 99           |
|                             | Sjogren A 169              | Wahren J 309         |
| Öberg K 223                 | Smith U 501                | Waldenstrom J 263    |
| Ødegaard A E 489            | Solling J 283              | Watz R 463           |
| Öman Rydberg A 253          | Solling K 283              | Wedel H 477          |
| Østergaard Kristensen B 511 | Solvell L 405              | Weening R S 233      |
| Ohlsson O 303               | Sørensen O H 391           | Wennevold A 115      |
| Ohm O J 153                 | Sorland S 375              | Werkö L 145 435      |
| Olin C 123                  | Sonnhaag C 245             | Wester P O 137       |
| Olsson H 319                | Sotaniemi E A 229          | Westlin N F 201 205  |
| Oosterhuis H J 131          | Stadl F 215                | Wetteland P 423      |
| Ornius E 127 289            | Stavenow L 197             | Wibell L 507         |
|                             | Stendahl O 451             | Wide L 361           |
| Palmblad J 241              | Stenius Aarniala B 417     | Wiklund P E 201 205  |
| Paulin S 145                | Stibler H 275              | Wilhelmsen L 337 447 |
| Pedersen Bjergaard O 193    | Storstein L 385            | Wilhelmsson C 477    |
| Pirkajarvi T 107            | Storstein O 161            | Wille L E 423        |
| Ponka A 77                  | Strander H 345             | Winnem, M 423        |
|                             | Stryland A 5               | Wise D 5             |
| Quist Paulsen A 489         | Strom S Suppl 633          | Wranne B 381         |
|                             | Svennerholm L Suppl 631    |                      |
| Rehfeld J F 215             |                            | Yhtalo P 107         |
| Rehnqvist N 169 299         | Tager J M 5                |                      |
| Reizenstein P 45            | Tegler L 21                | Zech L 321           |
| Reunanen M I 229            | Thulin T 303               | Zettervall O 31 37   |
| van Rhenen D J 233          | Tibblin G 337              |                      |
| Ringqvist I 253             | Tibblin L 381              | A see Aa             |
| Robinson D 5                | Tolagen K 303              | A see Ae             |
| Romer F K 27                | Tornvall G 123             | Ö see Oe             |
| H 375                       | Tukiainen P 417            | Ö see Oc             |
|                             | Turesson I 31 37           |                      |

315 MEDICAL COLLEGE,  
LIBRARY, 14328 JAIPUR

